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THE TREATMENT OF RENAL DISEASES*

BY

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Sir Walter Scott faced his last illness with the same fortitude and resolution as he had earlier shown in the financial straits to which he had been reduced by the brothers Ballantyne. In his journal we read: "Within these three days I have passed (you may alter the vowel A to the vowel I) a formidable quantity of blood. When a man makes blood instead of water, he is tempted to think of the possibility of his soon making earth." He makes no definite comment on the medical treatment which he received, but he probably did not expect much from it, for in connexion with the illness of a grandson he says, "I calculate upon his recovery with the greater certainty that I am well assured there is no medical man within reach."

I doubt if the lay attitude to kidney trouble has altered very much in the intervening years. An affection of the kidneys is still regarded as a death sentence which is not likely to be commuted by any doctor. In the lay mind, the kidneys seem to join the heart and brain in the inner circle of really vital organs, while the lethal potentialities of diseases of the lungs, liver, stomach, and blood-vessels are less seriously regarded. I would like here to examine how far lay people (and many doctors) are justified in associating renal disease with extreme gravity and with medical impotence.

I have chosen what I think is a natural and familiar title for my subject: but in actually dealing with it I would like to broaden the idea of "treatment" into that of management, and to discuss not the specific "renal diseases" but rather the symptom-complexes, or syndromes, which may be based on renal disease of widely differing aetiology. Sir Harold Himsworth (1949) drew attention to the "liberation of medical thought by the substitution of syndromes for 'disease entities' as the units of illness." His theme was diabetes mellitus; but a similar change in thinking has been equally productive in the study of renal disease. To quote further—for I know no better definition of the significance of the syndrome—"The syndrome, on the other hand, has its philosophical basis not in specific disease factors but in a chain of physiological processes, interference with which at any point produces the same impairment of bodily function. The same syndrome may thus arise from many different causes. This newer view inspires a far more catholic concept of aetiology and renders pointless many existing controversies."

This summarizes one aspect of the impact of applied physiology on clinical medicine. Since treatment is my theme, I may draw attention to another, even more practical, aspect of thinking in terms of syndromes. It often happens that we are either uncertain of the precise aetiology of a renal syndrome or else without power at present to correct its cause; but we can still do a great deal to mitigate the effects of the renal disorder on the patient's well-being. For example, a patient with massive renal oedema may be suffering from nephritis, from renal-vein thrombosis, from diabetic nephropathy, from lupus nephritis, to mention only a few of the possibilities whose clinical differentiation may be very difficult; but lack of certainty in aetiological diagnosis need not prevent us from treating the oedema, often with good effect. To say that we can treat our patients even when we do not know what is wrong with them is of course a dangerous half-truth; the treatment of a syndrome based on applied physiology, however efficient it may be, remains essentially palliative treatment, and in no way absolves us from prosecuting the search for a complete diagnosis. But the relief of symptoms is one of the classical aims of clinical medicine, and the concept of the syndrome has contributed materially to its fulfilment.

Space does not allow me to be either comprehensive or detailed. What I hope to do is to outline the principles of management of four syndromes of renal disorder which are commonly met with. I am supported in this endeavour by the substantial measure of agreement among nephrophiles, including those in other countries, as shown, for instance, in a recent German textbook of renal disease (Sarre, 1959). By remaining, as I hope, within the area of nephrologic agreement, I shall forswear the gloss of newness and the spice of controversy: but perhaps I may be able to help some doctor to help his patient with a renal disorder. My four topics will be acute renal failure, massive renal oedema, chronic renal failure, and acute urinary infection.

Acute Renal Failure

This term is preferable to its synonyms "anuria" and "suppression of urine," because complete failure to pass urine is most exceptional, and should indeed suggest an obstruction in the urinary tract rather than a renal disorder. Acute renal failure has its functional basis in a gross impairment of the renal circulation or, much less commonly, in the effect of various toxic agents. Its structural basis is a necrosis of tubular epithelium, with possibly some damage to the glomeruli as well. Clinically, there is a phase of extreme oliguria, commonly associated with haematuria, followed by a gradual increase in urine output with recovery. The inevitable consequence of acute renal failure is a progressive uraemia, which may be suspected clinically, but whose progress can be followed by blood-urea estimation. My reason for including this condition is not its frequency in general practice but its interest and general medical importance. In hospital practice, acute renal failure is being seen more often, as patients who would formerly have died from the shock of burns or trauma, or from an overwhelming infection, are now surviving as a result of resuscitation, accident surgery, and antibiotics. Medical causes of the syndrome include severe acute nephritis, the collagen diseases, papillary necrosis, leptospirosis, and haemorrhage or

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flux from the gastro-intestinal tract; acute renal failure may complicate abortion or accidental haemorrhage; and there is a trickle of iatrogenic renal failure from mismatched transfusion and drug reactions.

Recovery is possible in the majority of patients with acute renal failure who have a potentially reversible renal lesion. The crux of management is the maintenance of the patient in reasonable condition for the period of one to two weeks during which effective renal function is lacking. This is done by minimizing protein breakdown, and by preventing the intake of water and electrolytes which the patient cannot excrete. Protein breakdown is minimized by eliminating dietary protein; by giving 100 g. of carbohydrate, which will provide enough calories to bring the calorigenic breakdown of body-protein to a minimum; and by controlling infection and trauma, both of which lead to increased breakdown of protein. In patients with an involuting uterus, anabolic steroids have been shown to diminish the rate of protein breakdown. The intake of water and electrolytes must also be controlled. In a few patients, loss of fluid from the body has been the cause of acute renal failure; in these the loss must be made good.

In most patients there is no deficit of fluid, and any attempt to force fluids is highly dangerous; I would feel guilty of labouring the obvious, did I not still see patients who have been bloated with fluids, supposedly diuretic, to which their damaged kidneys cannot respond. The water intake is limited to 500 ml., and no salts are given; fruit juice should not be given, as it has a high potassium content. Since the "diet" contains only carbohydrate, vitamins of the B complex should be given; fats by mouth are nauseating, and we now usually leave patients to find their own fat from the body stores. Some patients will take 100 g. of glucose (or lactose) in 500 ml. of water in small doses by mouth; others prefer a gastric tube. When vomiting is serious—and this is less common when no fat is given—the mixture can be given by plastic catheter passed through the saphenous vein into the inferior vena cava. This purely conservative regime, introduced in its essentials just after the war by Borst and Bull, has been the most important single step in reducing the mortality from acute renal failure; and it remains adequate in "medical" patients.

The situation is very different in "surgical" patients. When tissue breakdown is accelerated by trauma, or infection, or the metabolic response to surgery, there are two main dangers. The rate of accumulation of nitrogenous waste products is increased severalfold; the increase in blood urea is a general measure of this, and urea itself has been found in animals to reduce survival rate (Grollman and Grollman, 1959) and to increase the irritability of the cerebral cortex (Stevenson *et al.*, 1959). More definitely, the release of potassium from traumatized or infected tissue can lead to a rise in the concentration of potassium in the plasma which may cause cardiac arrest. The hazard from potassium can be lessened by removing potassium from the body with exchange-resins; or by promoting a shift of potassium from the plasma into the cells of healthy tissue by measures such as giving insulin and glucose, or alkalis. The treatment which I have found most effective, apart from dialysis, in lowering the plasma potassium rapidly—and that is what is needed—is the intravenous infusion over a three-hour period of 200 ml. of molar sodium lactate. It is in this group of "surgical" patients, with accelerated breakdown of tissue, that dialysis with the artificial kidney can be life-saving. The value of and indications for dialysis have been reviewed by Parsons and McCracken (1959).

Massive Renal Oedema

This syndrome arises when urinary loss of protein, and especially of albumin, is so great and prolonged as to lead to severe hypoproteinaemia. This situation has been summed up in the phrase "protein-losing kidney" (Platt, 1959); and, as I have already indicated, its causes are multiple. The syndrome is often known as the nephrotic syndrome, but I prefer the more purely descriptive term which I have used, perhaps influenced by the trenchant comment of Jean Oliver (1950), that "nephrosis" means a condition in which the kidney is full of kidney. It is tempting to add the qualification "hypoproteinaemic," as indicative of the chief mechanism of this type of oedema; but economy and even elegance should have a voice in our terminology, in preference to the fear of missing something out which has coined so many burdensome titles.

While this type of renal disease is still serious, some progress has been made towards mitigating the discomforts and dangers which surrounded the patient twenty years ago. Very occasionally, a real cure can be effected in special cases—for example, by eliminating tuberculous infection which has led to renal amyloidosis, or by stopping teething-powders in children with mercurial nephropathy. Death from intercurrent infection can now be prevented by antibiotics; and there is some evidence that prophylactic treatment with oral penicillin may retard or prevent progress of the lesion. General measures for the long-term control of oedema have been reinforced by the development of effective oral diuretics. These are worth a trial in massive renal oedema, for some patients respond well; but they are not to be persevered with in patients with refractory oedema. As Rosenheim and Spencer (1956) have shown, when the oedema is controlled by a low-salt high-protein diet, supplemented by exchange-resins, about half the patients go into full clinical remission, with normal plasma-albumin levels and no significant proteinuria.

The control of oedema, and almost certainly the long-term prognosis of the syndrome, has been improved by the development of adrenal steroids of the glucocorticoid group which are almost free from any direct effect on the renal excretion of electrolytes. When cortisone was used, it was common to see a transient increase in oedema, followed later by a diuresis, often after the end of a 7- or 14-day course. This transient diuresis is not the important effect of steroids, which are used with the object of cutting short the proteinuria. With prednisone or prednisolone the frequency and speed of remission are greater than with simple control of oedema. The real test of success is disappearance of the proteinuria: steroids should be given until this happens, and continued for at least a month thereafter, to be resumed again if proteinuria should recur. The dosage should be low and intermittent—for example, 20 mg. of prednisone on four days each week. The dosage should not be increased in an attempt to control oedema, which should respond rather to diet and resins; I have seen striae and other signs of corticoid-poisoning from this

course of action. Nor should the dosage be continuous, as even prednisone produces some increase in potassium excretion, and breaks in the course allow the resulting potassium loss to be made good from the diet or from potassium supplements.

Some patients show severe hypertension or azotaemia soon after the apparent onset of their illness, and in these the prognosis has to be poor. Of the remaining majority, some will remit spontaneously if oedema and infection are controlled; but a greater number of remissions can be achieved with steroid treatment. The decision about steroid treatment may be difficult in the individual patient: renal biopsy may be helpful, for there is already some indication that a good response to steroids is much less likely in patients with established glomerular damage. At present, however, steroids should probably be given except in the two extreme situations of proteinuria without significant oedema and, on the other hand, advanced renal failure or hypertension.

Chronic Renal Failure

There are several reasons for preferring this term to the common "uraemia" or the slightly precious "azotaemia." Both these words have a chemical implication which is misplaced in the description of a clinical syndrome—especially if we reflect on the state, sometimes miscalled "acute uraemia," in which the blood urea is not greatly increased and the symptoms are probably due to hypertensive encephalopathy. Again, the chemical terms focus attention on failure of the excretory function of the kidney, to the exclusion of the regulatory function of the kidney; yet disturbance of the renal regulation of the amount and composition of body fluid lies at the root of many symptoms, and these are more amenable to direct treatment than the nitrogen retention, which can only be palliated by protein restriction. Interesting and important as it is, I cannot deal adequately with the complex chemical alterations in renal failure, many of which have been reviewed by Platt (1952); and it could indeed be claimed that chronic renal failure is not one, but a whole collection of syndromes. I shall concentrate my own remarks on two topics—chronic failure which is potentially reversible, and those measures of palliation which can be simply achieved.

Reversible Chronic Renal Failure

I have set out in a Table some of the causes of chronic renal failure which are reversible in their early stages, but whose neglect can lead to progressive renal damage. While the investigation and relief of obstruction of the urinary passages is the work of the urological surgeon, he cannot do it if he does not see the patient: it is the responsibility of the physician to remember that renal failure can have a "surgical" cause; to ask about prostatic symptoms and other disorders of urination; to feel for enlargement of the prostate, bladder, or kidney; and to refer selected patients for intravenous pyelography or full urological study. Chronic renal failure is not in itself associated with fever, except in its terminal stages; and the complaint of chills or dysuria, or the observation of pyrexia, at once raises the possibility of pyelonephritis or, more remotely, of renal tuberculosis or the nephropathy of bacterial endocarditis. Unfortunately, the suspicion of a renal infection may be hard to confirm, even with repeated urine cultures; and even when an infection has been demonstrated, it may still be hard to eradicate: but this need not stop us from trying to clear up infection with a short course of broad-spectrum antibiotics, judging our success by the alleviation of symptoms, if we have no better guide. Recurrent infection after treatment should stimulate the search for a local abnormality of the urinary tract; even though in most patients none will be found, the exceptions serve to approve the practice.

Some Causes of Reversible Chronic Renal Failure (Modified from Merrill, 1955)

Obstructive uropathy	Calculus Prostatic hypertrophy Urethral stricture and valve Periureteric fibrosis
Infection	Superimposed acute pyelonephritis
Metabolic	Hypercalcaemia: Milk-alkali syndrome Vitamin-D overdosage Sarcoidosis Hyperparathyroidism Potassium depletion Sodium depletion

Simple Palliative Measures

Comparatively few patients with chronic renal failure owe it primarily to deranged metabolism; but the possibility of treatment justifies some attention to this problem, and of course secondary disturbances of metabolism are very common in renal failure, whatever its primary cause. Most patients with renal failure have a low serum-calcium level, but in a few patients hypercalcaemia is present, and may be the cause of the trouble. Hypercalcaemia can occasionally be suspected when the intake of calcium and alkali, or of vitamin D, is known to be high; or when anorexia, vomiting, and mental disturbance are striking, though the blood-urea level is only moderately raised; or when there is great thirst and polyuria, or a metallic taste in the mouth, again at low levels of blood urea. Such a suspicion has to be checked by estimation of the serum calcium. If hypercalcaemia is established, full metabolic investigation is needed, so that dietary causes can be eliminated, the hypercalcaemia of sarcoidosis reduced by steroids, or a parathyroid tumour removed. Potassium and sodium depletion are less common than excess of calcium as primary causes of renal failure; also, a depletion sufficient to cause renal failure will be obvious on other grounds, which is not always so with hypercalcaemia. However, secondary depletion of sodium, and to a less extent of potassium, is common in renal failure, and warrants attention in management.

In dealing with patients with chronic renal failure, we must not be frightened by figures, and especially not by a blood-urea result obtained soon after the patient has been admitted in some form of crisis. A patient with a blood urea of 100 mg./100 ml. may be symptom-free, but he is very vulnerable. In a day or two he may become critically ill from the tissue breakdown in an acute infection, from the loss of fluid from a gastro-intestinal upset, or even from drinking too little (or too much) when his kidneys have lost their plasticity of regulation. When we see him in this state, as it seems of terminal illness, it is easy to give up, and regard any treatment as meddlesome interference. I believe this attitude is wrong, not because I have any interest in prolonging a life of misery, but because so many of these patients can be made symptom-free again. We can never tell without trial how much the illness of a patient with renal failure is due to permanent renal damage and how much to reversible extrarenal factors. The

principles of management are similar to those which I have described for acute renal failure, with one very important exception.

While a chief danger of acute renal failure is excess fluid, most patients in a crisis of chronic renal failure are short of fluid, because of deficient intake and often vomiting and diarrhoea. They tend to have a low serum sodium and are markedly acidotic, so it seems justified to give hypertonic sodium lactate intravenously. I have used 200 ml. of molar sodium lactate by drip, and if this brings down the blood urea and improves the patient's condition it can be repeated daily until the vomiting abates to allow treatment by mouth. This treatment with alkali may aggravate tetany, in which event calcium gluconate should be added to the infusion. In some patients chlorpromazine has seemed to diminish vomiting as well as apprehension: only about 10% of a dose of chlorpromazine is excreted normally in the urine, so the presence of renal failure does not compel any material modification of dosage.

While intercurrent episodes of infection or dehydration call for active management, the patient with chronic renal failure may at other times have few or no symptoms, and should not be subjected to niggling restrictions. These patients, especially if they are normotensive, can live for some years, and they should be allowed to do what they like. At any given level of renal insufficiency, the blood-urea level increases with the protein content of the diet. Excess of protein should be avoided, but a severely restricted protein intake is called for only in episodes of superimposed extrarenal uraemia. Salt restrictions should be avoided, except when hypertensive cardiac failure is imminent; and a few patients may even need large supplements of salt, in the "salt-losing" form of renal failure. Some patients may need potassium supplements, but this again is very exceptional, and the need must be established by a study of metabolic balance. In limiting myself to palliative measures which can be simply achieved, I am unfortunately compelled to omit any account of the remarkable symptomatic and objective improvement which can be achieved in the osteodystrophy of chronic renal failure (Stanbury, 1957).

Acute Urinary Infection

If the generality of patients are inclined, if anything, to overestimate the seriousness of nephritis in any of its forms, they make the opposite mistake with acute urinary infection. The usual lay term for acute urinary infection perhaps discloses this attitude—"a chill on the bladder," something accepted as a nuisance comparable to a cold in the head. But as a cause of chronic renal failure or of severe hypertension of renal origin, chronic pyelonephritis—the possible sequel of neglected acute urinary infection—is at least as important as glomerulonephritis.

I need scarcely describe the familiar symptoms of a typical attack of acute pyelonephritis. However, since clinical recognition is the necessary (but not sufficient) prelude to effective treatment, it may be worth mentioning two points which seem not to be universally recognized. One is that overt haematuria in a febrile illness may indicate acute urinary infection rather than acute nephritis or even bacterial endocarditis. The other is that dysuria and frequency may be so minimized that an acute urinary infection may present as a pyrexia of uncertain origin, or in infancy as a failure to thrive (James, 1959). Acute urinary infection is a common disorder, and the family doctor should have open access to the facilities needed for eliciting the essential sign—the demonstration of pus cells and organisms in the urine. I think we have an opportunity here for improving our practice of preventive medicine. It is more important to send the urine forthwith to the clinical laboratory than to arrange for the patient to attend an out-patient clinic, by which time the urinary sediment may have cleared and the chance of specific treatment been lost. I am not suggesting an orgy of domiciliary catheterization—there is too much evidence that infection can be introduced into the bladder in this way. In the male, a mid-stream specimen is satisfactory; in the female, a clean specimen after perineal swabbing can be used as a first screen, followed if necessary by a catheter specimen.

The key to treatment, as to diagnosis, lies in adequate bacteriological characterization of the infecting organism—and this of course includes assessment of its sensitivity to sulphonamides, antibiotics, or nitrofurantoin. Sensitivities can conveniently be tested by the disk technique (Fairbrother, 1959). The appropriate specific treatment can then be given. Whatever agent is chosen, the dosage must be adequate to give an effective concentration in the blood and tissues, as well as in the urine; for example, sulphadimidine should be given in a dose of 1.5 g. six-hourly, and not in the lower doses sometimes used. After a week of treatment a further specimen of urine should be examined, and a later specimen after specific treatment has been stopped for a few days. When relapse occurs with a sulphonamide-sensitive organism there may be a place for the long-acting drugs such as sulphaphenazole. Recurrent bouts of urinary infection justify a search by intravenous pyelography or by full urological investigation for local conditions of the urinary tract which would lead to stasis. The necessary procedures may include urethroscopy (Winsbury-White, 1959). Exemption from this search is, however, conferred by pregnancy.

I have said nothing of the palliative treatment of dysuria. Making the urine alkaline may indeed alleviate symptoms, but it does nothing to eradicate the infection. In a patient with impaired renal function the giving of alkalis is positively dangerous, since it may lead to a systemic alkalosis, or to potassium-poisoning when citrate of potassium is chosen. If the symptoms of urinary infection are definite it is better to give a soluble sulphonamide, once a urinary specimen has been taken for bacteriological examination. When the results of sensitivity tests are known the treatment may be changed to a broad-spectrum antibiotic or to nitrofurantoin, if indicated. In the absence of bacteriological facilities lack of response to sulphonamide may justify a similar change of treatment.

I have assumed that the energetic investigation and treatment of acute urinary infection would lessen the frequency of chronic pyelonephritis. Though this seems a reasonable assumption, I have to admit that I know of no adequate figures of the incidence of chronic pyelonephritis following an acute urinary infection, whether adequately treated or not—let alone any comparison designed to bring out the effect of treatment. May I end by pointing out that this would be a most useful investigation, and one which for several reasons could best be carried out in general practice. Acute

urinary infection is reasonably common in the community, but few patients in the acute attack enter the practice of a hospital. Strict criteria of diagnosis can be established, using the facilities available in any clinical laboratory. Given these facilities, treatment can be standardized, and its short-term success or failure can be established. Finally, the long-term result will become apparent only after many years, during which the patient will have no symptoms that would make repeated visits to a hospital for follow-up seem reasonable; but his family doctor could check his blood-pressure and examine his urine without any particular disturbance.

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THE INNERVATION OF SKELETAL MUSCLE*

BY

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[WITH SPECIAL PLATE]

Although our knowledge of the pattern of innervation of skeletal muscle and its functional significance is still incomplete, there is much that throws light on the problem of control of postural and so-called volitional movement. In this brief review attention will be confined to the nerve-supply of mammalian striated muscles and to the connexions that these neurones make in the central nervous system.

The Motor Unit

The smallest functional unit in a muscle is the motor unit, which consists of a single anterior horn cell, all its processes and all the muscle fibres supplied by it.[1 2] It follows that the strength of contraction depends, in part, upon the size of these motor units as well as on the number brought into activity.[3] Recent estimates of the average number of muscle fibres in human motor units range from 5–9 for extrinsic ocular muscles[4] to 1,600–1,900 for one of the calf muscles.[5] The endings of the motor nerves lose their myelin sheaths as they pierce the sarcolemma and break up into fine branches which rest in the shallow troughs that form the sub-neural apparatus.[6] These troughs are lined by structures which are rich in cholinesterase,[7] the enzyme that destroys acetylcholine, which is the chemical transmitter of the nerve impulse across the neuromuscular junction (Special Plate, Figs 1 and 2). The motor end-plates may be confined to a localized band or be scattered throughout the substance of a muscle. In some muscles —for example, the extrinsic ocular and facial muscles— more than one motor ending can be seen on a single fibre; and these end-plates are sometimes supplied by nerve fibres which approach from different directions.[8 9] Since motor nerve fibres not only branch in the main nerve trunks[3] and muscles,[10] but also may form intra-muscular plexuses (Special Plate, Figs. 3 and 4), histological preparations of healthy muscles do not give reliable evidence about the parent neurones of the divergent fibres. For larger muscles in which the physical difficulty of examining long fibres throughout their length is increased, there is only scant reference to histological evidence of multiple endings on a single fibre, but electrophysiological experiments have shown that large motor nerve fibres may innervate individual muscle fibres at two or more places.[11–13 17] These multiple endings may be derived from the branches of a single neurone or from several neurones. The muscle fibres of a unit may be in a compact bundle or they may be separated widely from each other and give rise to a diffuse motor unit.[8 10 14–17]

Whatever the spatial arrangement of the motor units within the muscle belly, however, there is anatomical and physiological evidence that the motor nerve cells supplying individual muscles are grouped together in the brain-stem and spinal cord, where they form nuclei.[18–26] Sharrard[23] reconstructed the lumbar and sacral segments to scale from serial sections of three normal spinal cords and of seven from patients who died at intervals ranging from three months to eight years after the onset of anterior poliomyelitis. The reconstructions took no account of the dendrites and axons, but gave the relationships between the bodies of the anterior horn cells. By correlating the histological and clinical observations it was possible to demonstrate the arrangement of the nuclei supplying individual muscles. These nuclei varied in size; some occupied several segments of the cord, while others were confined to a single segment, and functionally related nuclei were anatomically related to each other. Thus the nuclei supplying the tibialis anterior and posterior muscles were contiguous. Both these muscles invert the foot; the former dorsiflexes the ankle-joint and the latter plantar-flexes it.

The lower motor neurones which activate the motor units form the "final common pathway"[27] between the central nervous system and the muscles, and once they degenerate there is no longer any effector pathway between the central nervous system and the muscle fibres. Anterior horn cells have many dendrites which lie inside and outside the grey matter of the cord[28 29] and these processes account for the greater part of the total surface area of the cells,[30] thus increasing the area for contact with the "end feet," or *boutons terminaux*, of other neurones. It is through these *boutons* that neurones from other levels of the nervous system exert their influence on the lower motor neurone. It has been estimated that about 80% of the surface of an anterior horn cell is related to the *boutons*,[31] at least 2,000 of which may rest on the surface of a single large cell in the cat.[29 31 32] This does not necessarily mean that there are synaptic connexions with 2,000 other neurones, for the nerve terminals branch, and many of the *boutons* might be derived from one parent cell. The *boutons* vary in size, but even with electron microscopy it has not proved possible to distinguish

*A paper read to the Section of Anatomy and Physiology at the Annual Meeting of the British Medical Association, Birmingham, 1958.

between the excitatory and inhibitory endings that physiological evidence has shown to exist.[32–34]

Conduction of Impulses

Muscles are not only activated and influenced by the central nervous system, but they are also a source of incoming sensory stimuli. In a so-called motor nerve, for example, supplying a limb or trunk muscle, at least 30–40% of the fibres are sensory in function and have their cell bodies in the dorsal root ganglia of the segmental nerves.[1–3] The diameter of these afferent fibres ranges from 1μ to 20μ,[3 35] and the spectrum of fibre sizes has three peaks—Group I (12–20μ), Group II (4–12μ), and Group III (1–4μ).[35 36] The rate of conduction of impulses varies from 1 to 125 metres per second; and the full extent of the range is stressed when the rate of conduction is given as about 2¼ miles (3.6 km.) per hour for fibres of the smallest diameter and 280 miles (450 km.) per hour for those of the largest diameter.

The endings of afferent fibres in muscle vary enormously in structure. The simplest are very fine, non-myelinated nerve fibres with no specific endings. Some run in perivascular plexuses (Special Plate, Fig. 5), others are found in connective tissue, and it has been suggested that these are pain fibres.[37 38] More complex encapsulated Pacinian corpuscles (found also in skin and the mesentery) are described. These clearly are not specific to muscle; indeed, they are hard to find,[37 39] but when found they are related to deep fascia, to aponeuroses, and to intramuscular vessels and nerves (Special Plate, Fig. 6); they are supplied by large, fast-conducting nerve fibres. In the mesentery they have been found to respond to mechanical stimuli,[40] but their function in muscles has yet to be analysed.

The third variety of sensory ending is presumably stimulated by contraction of single muscle fibres. Large-, medium-, and small-diameter nerve fibres form claw-like endings, spirals (Special Plate, Figs. 7, 8, 9), and basket-like networks round individual muscle fibres. These forms of sensory ending have been found in extrinsic ocular muscles[41] and those of the face[9 42] and larynx.[42]

More is known about the fourth and fifth types of sensory end-organ, which constitute built-in automatic damping-down and alerting mechanisms in striated muscles.[44] Golgi tendon organs are inhibitory in function,[45 46] and are arranged in series with the muscle fibres[2 46] and are close to the insertions of the spindles which constitute the alerting mechanism.[37] In tendon organs the terminal branches of large, fast-conducting nerve fibres lie at the musculo-tendinous junctions, and the spray of endings constitutes either the whole or part of a sensory unit (Special Plate, Fig. 10). The size of these units and their relation to individual motor units are unknown at present. The frequency with which the tendon organs fire off impulses is a measure of the tension developed within the muscle either by active contraction or by passive stretch.[47] Through a reflex pathway in which there is an interposed connecting neurone these organs exert an inhibitory effect upon the anterior horn cells which innervate their own and functionally related muscles.[45 48]

Muscle Spindles

The muscle spindles are encapsulated, vary in complexity, and have both motor and sensory nerves.[1 37 49 50] In man they have been found in muscles of the face, larynx, palate, and infrahyoid region, in extrinsic ocular muscles, in the tongue, in the muscles of trunk and limbs, and in the striated upper third of the oesophagus.[41–43 51–54] So far they have not been found in muscles of the pharynx or the anal and urethral sphincters, which are still being investigated. They may occur singly or in groups,[39 51 56] and in man are more numerous per unit volume of muscle in the intrinsic muscles of the hand and in muscles of the neck than in the large limb muscles.[52] They are probably most plentiful in postural muscles, and nearly as numerous in flexors used for delicate movements.[56] Some indication of the density of the spindle population can be gained from the fact that 47 were found in the inferior rectus and as many as 71 in the superior oblique muscle in man.[52 55] In the cat 45 spindles were found in the soleus, 57 in the gastrocnemius, and 58 in the tibialis anterior.[39]

Spindles are fusiform and may even be visible to the naked eye—for example, a single spindle from the vastus medialis in a rabbit measured 3.6 mm.,[37] and in the intrinsic muscles of the human hand they ranged from 3 to 12 mm. in length.[53] The muscle fibres inside a spindle are known as the intrafusal fibres and are of two distinct sizes. It is suggested that the larger intrafusal fibres are of the fast twitch variety, and that the smaller ones, like red muscle fibres, are slow and tonic in their contractions[50] (Special Plate, Fig. 14). The largest extend from end to end of the spindle, and may pass right through one into another, forming tandem spindles[53]; the narrowest fibres are inserted into the capsule.[37] The smallest spindles contain one fibre, but as many as twelve have been reported.[53] Intrafusal fibres differ from the extrafusal ones in several respects (Special Plate, Figs. 11 and 12): they are usually narrower in diameter, stain differently, are more faintly cross-striated, and have centrally placed nuclei, which, in the larger intrafusal fibres, become so numerous halfway along the length of a spindle that this equatorial region is also known as the "nuclear bag" (Special Plate, Fig. 13). In the nuclear bag the sarcoplasm is much paler and the cross-striation becomes so faint that

DESCRIPTION OF SPECIAL PLATE

FIG. 1.—Motor end-plates in gracilis of rhesus monkey. (Gold chloride stain.* ×250.)

FIG. 2.—Subneural apparatus (marked by arrows) in diaphragm of rat. (Couteaux's modification of Koelle's stain. ×110.)

FIG. 3.—Intramuscular plexus formed by trigeminal and facial nerves in facial muscle of rhesus monkey. (Gold chloride stain. ×68.)

FIG. 4.—Intramuscular plexus in rabbit's interosseus muscle. Note scattered motor end-plates. (Gold chloride stain. ×68.)

FIG. 5.—Perivascular plexus in rabbit's interosseus muscle. *a*=nerve trunk from which a fibre (*b*) enters the plexus. (Gold chloride stain. ×68.)

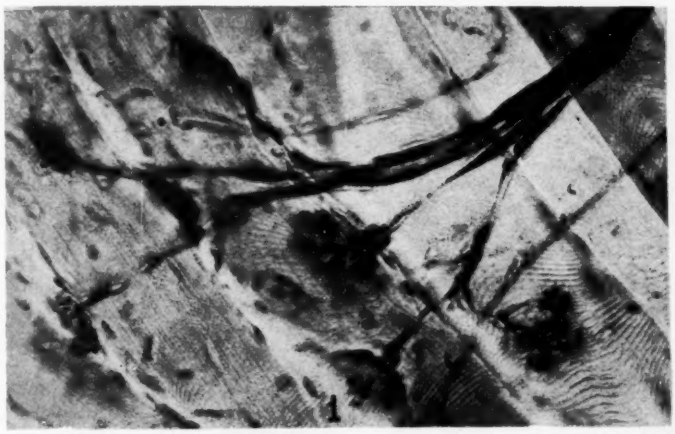
FIG. 6.—Pacinian corpuscles (P.C.) related to neurovascular bundle in cat's interosseus muscle. A=an arteriole. (Gold chloride stain. ×30.)

FIG. 7.—Transverse section of sensory endings (*a*) in medial rectus muscle of man. (Romanes's silver stain. ×200.)

FIGS. 8 and 9.—Longitudinal section of spiral sensory endings in medial rectus muscle of man. (Romanes's silver stain. ×200.)

FIG. 10.—Golgi tendon organ in cat's interosseus muscle. (Gold chloride stain. ×68. Preparation by Miss B. Higgs, B.Sc.)

*For details of gold chloride stain see *J. Anat. (Lond.)*, 1956, **90**, 217.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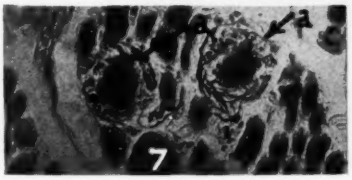
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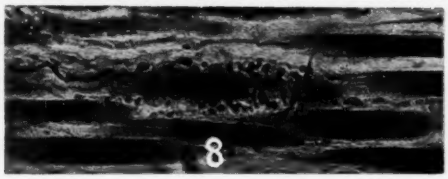
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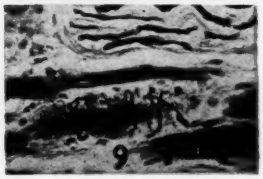
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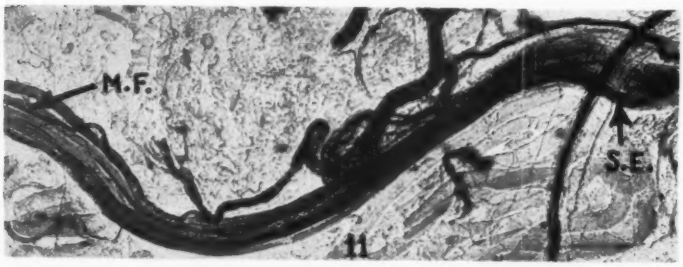
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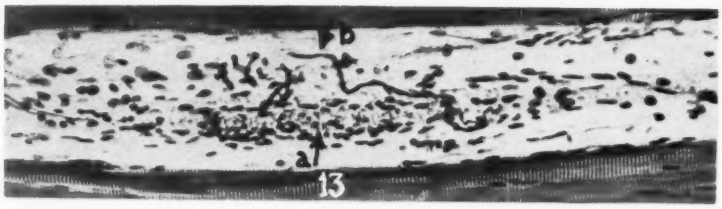
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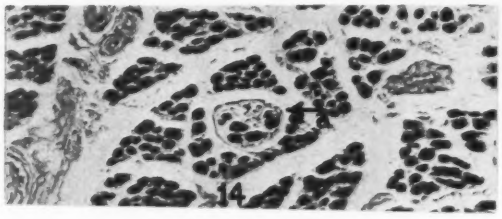
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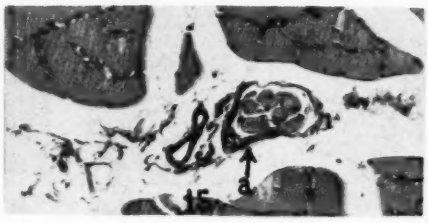
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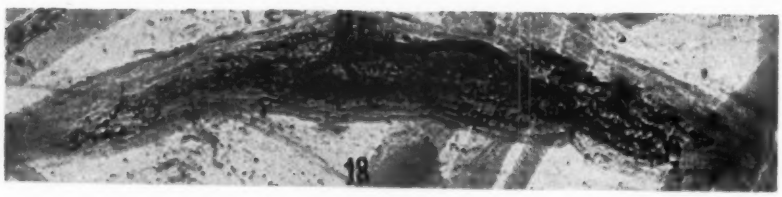
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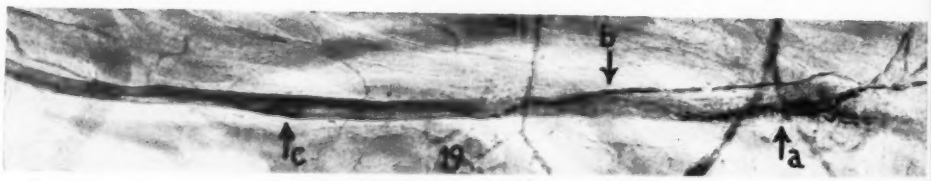
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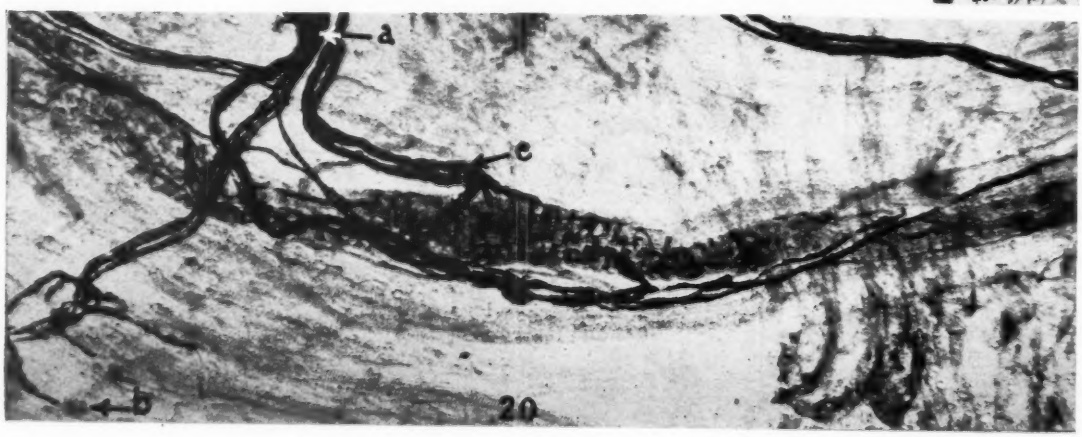
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in some histological preparations it appears to be lost. In the narrowest fibres the nuclei form a chain in the equatorial region.[50]

The capsule may consist of a single layer of connective tissue or of several layers (Special Plate, Figs. 14 and 15). It has been suggested that the more numerous the layers of the capsule the greater its protective function, but it is possible that this layering is a means of grading the response or of reducing the sensitivity of the sensory endings.[52] Since the spindles lie in parallel with the muscle fibres, they are extended when the muscles lengthen and are relaxed when they shorten; but as the intrafusal fibres have a motor nerve supply their tension can be altered by contraction of the intrafusal fibres themselves.

Innervation of Muscle Spindles

The pattern of innervation of the spindles is still being studied, but certain facts are well established. There are several motor end-plates on each pole of an intrafusal fibre[37 53] (Special Plate, Fig. 16), and the nerve fibres which supply them are slow-conducting (20–44 metres per second) gamma fibres of 3–8 μ in diameter.[57 58] These arise from the small cells of the anterior horns of the cord, leave by the anterior roots of spinal nerves, and constitute about one-third of the total number of motor fibres destined for skeletal muscle.[3 17] The small motor fibres branch and therefore form spindle motor units (Special Plate, Fig. 17). A single nerve fibre and its branches may supply each pole of one intrafusal fibre, and also may innervate other fibres of the same and different spindles.[37 39] It is also known that the fibres of a single spindle may be innervated by more than one spinal segment.[39] One pole of a spindle may receive additional larger, and therefore more rapidly conducting, motor fibres[37 47 53 56] (Special Plate, Fig. 19).

DESCRIPTION OF SPECIAL PLATE

FIG. 11.—Part of muscle spindle in cat's interosseus muscle. Note the narrower and more darkly staining intrafusal muscle fibres. M.F.=the fine motor nerve fibre supplying two motor end-plates on a single muscle fibre; S.E.=the sensory endings supplied by a thick nerve fibre. (Gold chloride stain. ×68. Preparation by Miss B. Higgs, B.Sc.)

FIG. 12.—Longitudinal section of sartorius muscle of rhesus monkey, showing the polar region of a spindle with narrow, more palely staining muscle fibres. (Romanes's silver stain. ×100.)

FIG. 13.—The nuclear bag or equatorial region (*a*) of the same spindle as Fig. 12. Note *b*, the thick sensory nerve fibre forming part of the annulo-spiral ending. (×182.)

FIG. 14.—Transverse section of medial rectus muscle (man). Note *a*, the single layer of the sheath of a muscle spindle with seven intrafusal fibres of large and small diameter. (Romanes's silver stain. ×200.)

FIG. 15.—Transverse section of cat's soleus. Note layering of capsule (*a*) of spindle. (van Gieson's stain. ×152.)

FIG. 16.—Multiple motor end-plates (marked by arrows) on intrafusal muscle fibres in rabbit's interosseus muscle. (Gold chloride stain. ×178.)

FIG. 17.—Gamma motor fibre (3.8 μ) dividing at *a* in the spindle shown in Figs. 12 and 13. Four branches could be found by focusing up and down; only three show in the plane of the photograph. (×200.)

FIG. 18.—Elaborate annulo-spiral ending in large spindle in rabbit's tibialis anterior. (Gold chloride stain. ×173.)

FIG. 19.—Spindle in rabbit's interosseus muscle. Note (*a*) simple annulo-spiral ending; (*b*) medium-sized motor fibre ending at *c*. (Gold chloride stain. ×100.)

FIG. 20.—Part of a spindle in sartorius muscle of rhesus monkey. Note (*a*) an intramuscular nerve trunk supplying extrafusal motor end-plates (*b*) with medium-sized fibres and (*c*) the large-diameter fibres forming the annulo-spiral endings. (Gold chloride stain. ×200.)

However, this is denied by some workers,[58] and the significance of the observation is obscure. Although the motor supply of both intrafusal and extrafusal fibres may run in the same intramuscular nerve trunk (Special Plate, Fig. 20), there is some doubt whether one axon ever supplies both types of muscle fibre.

The sensory fibres have their cells of origin in the dorsal root ganglia of the segmental nerves, and their peripheral endings are either at or near the equatorial region. The most elaborate annulo-spiral or primary endings are formed by the largest myelinated fibres (12–20 μ diameter), which are wound round the equator of the intrafusal fibres (Special Plate, Figs. 18 and 20). Other more diffuse flower-spray or secondary endings are formed by medium-sized fibres, and there may be one, two, or none in the spindle. When annulo-spiral and flower-spray endings are found together the latter lie to the side of the nuclear bag.[37 50] Both types of ending are stimulated by deformation due to a change in the shape of the contractile intrafusal fibres.

A constant stream of impulses, of frequencies ranging from 10 to 60 per second, are transmitted by the γ motor fibres to the intrafusal fibres. These contract, and, while they add nothing to the tension of the muscle as a whole, they prime the sensory endings to fire off when a critical level of distortion is reached. When stimulated effectively the large fibres conduct impulses back to the spinal cord through the dorsal roots at rates ranging from 60 to 125 metres per second (216–450 km. or 135–280 miles per hour). The central processes of these nerves end directly on the anterior horn cells supplying their own and functionally related muscles. These sensory fibres constitute the afferent arc of the stretch reflex. There is the minimum synaptic delay, since there is no internuncial or connector neurone in this reflex pathway. By means of a branch working through an internuncial neurone these same afferent fibres inhibit the contraction of their antagonistic muscles.[33 45 59] The activity of spindles is not only enhanced by activity within muscles, but also by impulses carried to the anterior horn cells from higher levels of the central nervous system.[60–62] It is damped down or inhibited by the cut-out mechanism provided by the Golgi tendon organs[45] as well as by inhibitory impulses from other levels of the nervous system.[61 62]

Sensory Supply of Trunk and Limb Muscles

The sensory supply of trunk and limb muscles provides the afferent arc of a spinal reflex pathway for the adjustment of the activity of the lower motor neurones. The precise afferent pathways for muscles supplied by cranial nerves are not yet known, but it is clear that these lower motor neurones in the brain-stem as well as those in the spinal cord are under the influence of higher levels of the nervous system. However, careful search has so far failed to demonstrate any afferent projection pathway from the muscles to the cerebral cortex. This, at first sight, is surprising in the light of the many movements which require delicate gradation of muscular activity. On the other hand, the capsules of joints have a rich sensory innervation, and a projection pathway from joints to cerebral cortex has been found in cats.[63–65] Therefore, since the position of joints is signalled to the cortex, and this position, in any movement, is the result of muscular activity, there is, in effect, an indirect cortical representation of the muscles.

Grateful thanks are due to the National Foundation for Infantile Paralysis Inc.; to my colleague Dr. Charles

Downman for helpful criticism; to Mr. William Matthews for technical assistance; to Mr. F. Ellis, Miss J. Cherry, and Messrs. J. M. Crane and V. Willmott for the photography; and to the Editor of the *Journal of Anatomy* for permission to use Fig. 20.

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METABOLIC AND ENDOCRINE ASPECTS OF DIABETIC NEPHROPATHY

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In the past few years various metabolic and endocrine disturbances have been described in association with the specific vascular lesions of diabetes—namely, retinopathy and nephropathy. It is claimed that many of these disturbances have a pathogenic relationship with the development of the vascular complications.

Becker (1952) gave evidence of excessive adrenal cortical function in diabetics with retinopathy and Kimmelstiel–Wilson (K.W.) lesions. He noted an apparent relationship between the lipoid-laden vacuolated cells in the zona fasciculata of the adrenal cortex and the K.W. lesions in the kidney. A picture similar to early diabetic retinopathy and the K.W. lesion could be produced in alloxan-diabetic rabbits by the injection of corticotrophin or cortisone. Becker, Allen, *et al.* (1954), Becker, Maengwyn-Davies *et al.* (1954), and Maengwyn-Davies (1956) gave further evidence of excessive production of adrenal glucocorticoids in patients with diabetic retinopathy.

Becker *et al.* (1953) also reported a disturbance of vitamin B_{12} metabolism in patients with diabetic retinopathy. Using the vitamin B_{12} excretion test, they found that diabetics with retinopathy cannot retain the vitamin, while those with no retinopathy retain most of the given dose. However, Field *et al.* (1957) could not find a definite relationship between the development of degenerative complications of diabetes and the excretion patterns of the B vitamins.

A disturbed carbohydrate metabolism has been found in patients with clinically evident K.W. syndrome. Thus, Berkman *et al.* (1953, 1954), in a study of the serum polysaccharides in diabetics and non-diabetics, reported an increase in the total serum polysaccharides in diabetics with degenerative vascular complications, the highest level being observed in those with clinically evident nephropathy (Adlersberg *et al.*, 1956). It is not clear whether this increase is due to the renal impairment and is thus the result of the diabetic nephropathy, or whether it precedes the nephropathy and provokes the pathological lesions in the kidneys.

Mann *et al.* (1949) have noted hypercholesterolaemia in association with diabetic glomerulosclerosis. Later,

*Part of a thesis submitted by M. S. Sabour for the degree of Doctor in Medicine.

Barr and Russ (1951), Engelberg *et al.* (1952a, 1952b), Keiding *et al.* (1952), and Collens *et al.* (1954) studied the serum lipids, lipoproteins, and cholesterol levels in diabetics and their relationship to degenerative vascular complications, and found that the serum cholesterol and phospholipid levels were usually raised. The most striking finding, however, was an increase of the S_f 12-20 class of lipoproteins in the serum of patients with diabetic nephropathy out of proportion to the raised level of cholesterol.

The similarity between the pathology of diabetic nephropathy and diabetic retinopathy (Ashton, 1951) has facilitated the study of the various metabolic and endocrine aspects of these two complications. However, Volk (1956) has pointed to a dissimilarity between the retinal micro-aneurysms and the glomerular nodules in diabetes. In his opinion there are probably basic differences in the pathogenesis of the two lesions, so that the results obtained from the study of one lesion may not be applicable to the other.

In a thorough study of diabetic nephropathy, including needle biopsy of the kidney, we have obtained some interesting data about the endocrine and metabolic aspects of this condition. We were also able to investigate human diabetics without having to rely on the ophthalmoscopic changes as an indication of the renal changes.

Material and Methods

Sixty-five diabetic patients were fully studied both clinically and by laboratory methods, and by renal biopsy whenever possible. The following laboratory studies were done for every patient: (1) a complete examination of urine; in cases with proteinuria the amount of protein per 24-hour specimen was estimated, using Esbach's reagent; (2) urine culture to detect infections of the urinary tract; (3) stool examination; (4) total and differential serum protein patterns; (5) Hb, W.B.C., and other haematological investigations when indicated; (6) serum cholesterol; (7) blood urea and urea clearance test; (8) oral 50-g. glucose-tolerance test; (9) serum sodium and potassium, by flame photometry; (10) 17-ketosteroids in the urine, estimated by the Zimmermann reaction in 37 cases; (11) 17-hydroxycorticosteroids in the urine, estimated by the Silber and Porter (1954) method in 28 patients; (12) total non-glucosamine serum polysaccharides were estimated in 39 cases, using the anthrone reagent, according to the method of Graff *et al.* (1951); (13) the vitamin B_{12} retention test was done in 13 diabetics, 2 normal subjects, and a patient with pernicious anaemia, the vitamin B_{12} being estimated chemically (Boxer and Rickards, 1951); (14) the Thorn eosinophil test was done on nine patients four hours after the administration of corticotrophin.

Results

The diabetic patients were classified into four groups, according to the clinical findings. The 56 patients for whom adequate data were available were grouped as follows:

Group D1, comprising 15 patients who showed not a single complication of diabetes except occasionally diabetic ketosis and the polyneuritis which accompanied it. Laboratory findings were not taken into account until two weeks after control of the ketosis, if present.

Group D2, comprising 20 patients who showed arteriosclerotic complications — palpable tortuous superficial arteries, impending or actual senile gangrene, or coronary artery disease. This group also included cases that showed arteriosclerotic but not diabetic or hypertensive fundus changes, as well as cases of diabetic neuropathy.

Group D3, comprising two patients with diabetic retinopathy, with no clinical evidence of renal involvement (no proteinuria).

Group D4, comprising 19 patients with proteinuria as evidence of diabetic nephropathy. All showed diabetic retinopathy as well, and most of them had arteriosclerotic and neuropathic complications.

Serum Proteins.—The total serum protein levels, the serum albumin levels, and the serum globulin levels in the four groups are shown in Figs. 1, 2, and 3. The cases within group D4 with heavy proteinuria and with the nephrotic syndrome showed the lowest serum albumin levels.

Serum Cholesterol.—The serum cholesterol levels are shown in Fig. 4. The mean value in group D1 is 190.4 mg./100 ml., in group D2 237.7 mg./100 ml., in group D3 243 mg./100 ml., and in group D4 251 mg./100 ml. The highest value was 390 mg./100 ml. in a patient in group D4.

Serum Sodium.—Fig. 5 shows the serum sodium levels in the four groups. Groups D1 and D2 showed a

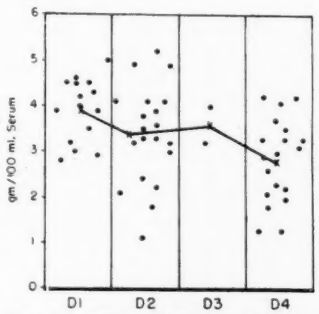

FIG. 1.—Serum albumin in diabetics.

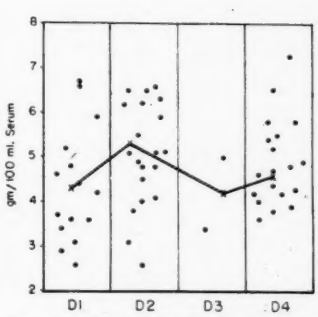

FIG. 2.—Serum globulin in diabetics.

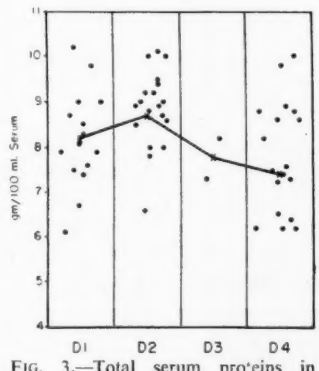

FIG. 3.—Total serum proteins in diabetics.

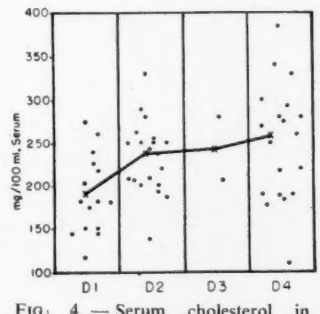

FIG. 4.—Serum cholesterol in diabetics.

normal serum sodium; while group D3 and especially group D4 showed a low serum sodium level (mean 131.5 mEq./l.).

Serum Potassium.—Fig. 6 shows the serum potassium levels in the four groups. In Group D1 the level was slightly lower than the average normal, but was still within the normal range. Group D2 showed a slight rise above the average normal value. An especially well-marked rise was seen in group D4, with a mean value of 5.75 mEq./l. Two of them showed values of 7 mEq./l.—the highest value seen among the 56 patients investigated.

Serum Polysaccharides.—The total serum polysaccharides were estimated in 8 normal subjects, and 31 diabetic patients. The normal individuals were taken from the donors to the blood bank of the hospital, all being males. Of 31 diabetic patients 7 were in group D1, 11 in D2, 2 in D3, and 11 in D4. The total serum non-glucosamine polysaccharides as determined by the anthrone reagent had an average normal value of 149.4 mg./100 ml. serum. In group D1 the average value was 146 mg./100 ml.; in group D2, 158; in group D3, 190; and in group D4, 258 mg./100 ml. (Fig. 7).

Urinary 17-Hydroxycorticosteroids.—These were estimated in 28 diabetic patients according to the method of Silber and Porter (1954): 9 were in group D1, 8 in group D2, 1 in group D3, and 10 in group D4. The average value in each group was 7.5, 13.5, 21, and 23.5 mg. respectively (Fig. 8). The following interesting fact was discovered accidentally. When the urinary 17-hydroxycorticosteroids were estimated in the first two cases very high values were obtained—38 and 34 mg. respectively. The result was questioned and the estimation was repeated some two weeks later, the values then being 8.5 and 11 mg. respectively. It was then realized that the patients had been admitted in diabetic ketosis and that the test was first performed while they were still in this state. After two weeks in hospital this defect was corrected, the diabetic state was stabilized, and consequently the level of the 17-hydroxycorticosteroids was much lower. This finding was later confirmed, for in three other patients admitted in ketosis the levels of 17-hydroxycorticosteroids were found to be 27, 33, and 24 mg.; and two weeks later the figures were 9, 5.1, and 16 mg. respectively. For the purposes of this analysis the results obtained from the patients during ketosis were ignored.

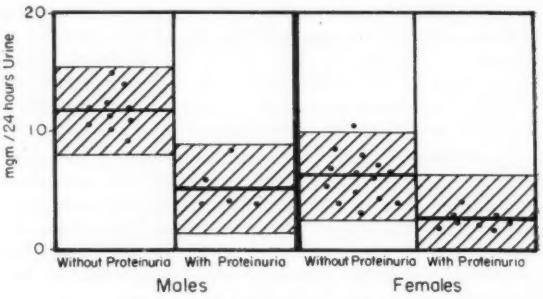

FIG. 9.—17-Ketosteroids in diabetics.

Urinary 17-Ketosteroids.—Urinary 17-ketosteroids were estimated in 15 male and 22 female patients, all adults. In the 10 males without diabetic proteinuria the average urinary excretion of 17-ketosteroids was 11.9 mg./24-hour specimen, and in the five males with diabetic proteinuria it was 5.3 mg. In the 14 females with no proteinuria the average daily excretion was 6.3 mg. and in the 8 females with diabetic proteinuria it was 2.5 mg. (Fig. 9). In four patients (two males and two females) the urinary 17-ketosteroids were estimated on two occasions—during ketosis and two weeks after control of diabetes. In the males the figures were 3 and 3.5 mg. during ketosis, and 15 and 14.1 mg. after control. In the females the corresponding figures were 2.7 and 1.0 mg. during ketosis and 5.3 and 4.3 mg. after control.

Vitamin B_{12} Retention Test.—This was done in 16 cases (13 diabetics, 2 normal subjects, and one patient with pernicious anaemia). The vitamin B_{12} content of the urine was estimated by the chemical colorimetric method described by Boxer and Rickards (1951). The eight-hour urinary output was ascertained, then 100 μg. of vitamin B_{12} was given intramuscularly, and the urinary output in the next eight hours measured. The difference was calculated as the percentage excretion from the given dose. The results are shown in Table I. which also records the results of renal biopsy. The excretion in the diabetic patients varied widely, yet the presence or absence of degenerative changes seemed to have some interesting effects on the figures. In Cases 4–9 there were no manifestations of degenerative changes, but all of them showed a marked degree of retention of

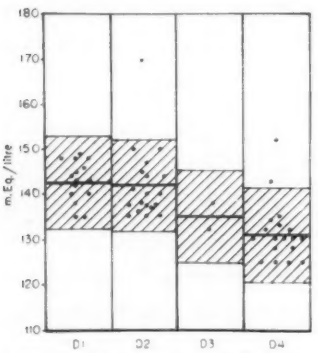

FIG. 5.—Serum sodium in diabetics.

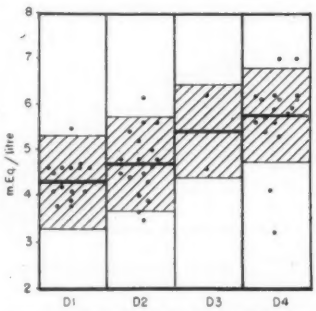

FIG. 6.—Serum potassium in diabetics.

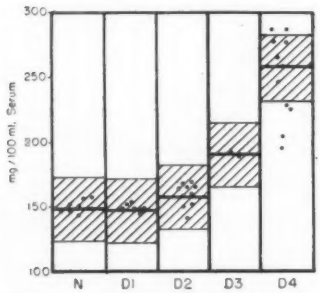

FIG. 7.—Total serum polysaccharides in diabetics.

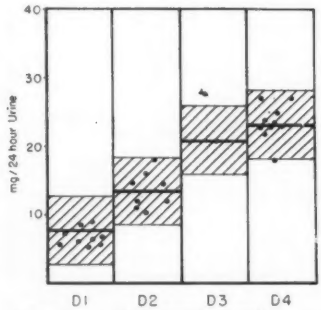

FIG. 8.—Hydrocorticosteroids in diabetics.

TABLE I.—*Results of Vitamin B_{12} Retention Test and of Renal Biopsy*

Case No.	Diagnosis	Excretion after 100 μg. vit. B_{12}	Clinical Degenerative Changes	Renal Biopsy
1	Normal	19%	None	
2	,,	17%	,,	
3	Pern. anaem.	3·3%	Polyneuritis	
4	Diabetes	9%	None	No lesion detected
5	,,	5·2%	,,	,, ,, ,,
6	,,	4·2%	,,	,, ,, ,,
7	,,	6%	,,	,, ,, ,,
8	,,	49·4%	,,	,, ,, ,,
9	,,	32·4%	,,	
10	,,	47·6%	Coronary sclerosis	
11	,,	27·2%	Arteriosc. ret. and neur.	
12	,,	21·5%	D. retin. and nephropathy	Glomerulosclerosis without hyaline fibrinoid lesions
13	,,	69%	,, ,,	Glomerulosc. and H.F.L.
14	,,	82%	,, ,,	,, ,, ,,
15	,,	71%	,, ,,	,, ,, ,,
16	,,	58·7%	,, ,,	,, ,, ,,

the given dose, with the exception of the last two cases, which were in a state of ketosis when the test was done. Cases 10 and 11 had degenerative changes but no nephropathy, and in these there was a moderate increase in the excretion of vitamin B_{12} compared with the normal. In Cases 12–16 diabetic nephropathy was present. The excretion of vitamin B_{12} was very marked in all of them, ranging from 58.7% to 82%, with the exception of Case 12 in which renal biopsy showed none of the hyaline fibrinoid lesions found in all the other cases. The results are summarized in Table II.

TABLE II.—*Summary of Results of the Vitamin B_{12} Retention Test*

Normal	Uncomplicated Diabetes		Diabetes with Degenerative Complications Other than Ret. and Neph.	Diabetic Nephropathy		Pernicious Anaemia
	Controlled	In Ketosis		No H.F.L.	With H.F.L.	
19 μg. 17 ,,	5·2 μg. 4·2 ,, 9·0 ,, 6·0 ,,	32·4 μg. 49·4 ,,	47·6 μg. 27·2 ,,	21·5 μg.	69 μg. 82 ,, 58·7 ,, 71 ,,	3·3 μg.

Thorn Test.—The four-hour Thorn eosinophil test was performed in nine patients (four without proteinuria and five with diabetic proteinuria). All nine showed a drop in the eosinophil count of more than 50%, indicating intact glucocorticoid function of the adrenal glands. However, it should be noted that in patients with diabetic proteinuria there was a greater drop (Table III).

TABLE III.—*Drop in Eosinophil Count Four Hours After 25 Units of Corticotrophin Intramuscularly in Nine Diabetic Patients*

Without proteinuria	..	57%	50%	60%	58%	
With diabetic proteinuria	..	86%	75%	83%	100%	100%

Discussion

Serum Proteins

Patients with diabetic nephropathy showed hypoalbuminaemia and hyperglobulinaemia; the total serum protein level was not always diminished, and seemed to depend upon the degree of diminution in the serum albumin or of elevation in the serum globulin.

Hypoalbuminaemia in diabetic nephropathy was recognized long ago, and was described with the nephrotic syndrome accompanying diabetic glomerulosclerosis (Newburger and Peters, 1939). The fall in the serum albumin level was regarded as secondary to the heavy proteinuria and excessive loss of serum albumin in the urine. This explanation cannot be accepted as the only mechanism of hypoalbuminaemia, since a fall in the serum albumin was noted in diabetic patients with degenerative complications (group D2) and in patients with diabetic retinopathy (group D3) in the absence of proteinuria. However, proteinuria was found in cases with the lowest levels of serum albumin (group D4).

Similarly, a rise in the serum globulin above the maximum normal value of 3 g./100 ml. was noted in all groups of diabetic patients, but especially in those with degenerative complications. These findings point to a disturbed metabolic pattern of the serum proteins in diabetics, which is especially exaggerated in those with degenerative complications, and may be responsible for the development of these complications in some way or other.

It has been suggested that shifts in the serum proteins play a part in the development of the degenerative vascular lesions seen in long-standing diabetics (McManus, 1950b; Friedenwald, 1952; Root, 1952). Schneider *et al.* (1946) described changes in albumin and β-globulin fractions of the serum from 31 diabetic patients with retinitis. The reduction in albumin and the elevation of the β-globulin fractions were more marked in the retinitis cases than in uncontrolled diabetics. Rifkin and Petermann (1952) reported the results of electrophoretic study of the serum proteins in patients with clinically established diabetic glomerulosclerosis. A decrease in the albumin and a significant rise in the α_2-globulin were found in all of their 10 cases. The β-globulin was normal or only slightly raised. Keiding (1954), using paper electrophoresis, found a definite decrease in albumin and α_1-globulin, and an increase in α_2-globulin in all diabetics, but only those with retinitis proliferans and proteinuria showed a diminution in total protein. The β-globulin remained unchanged.

It is concluded that the disturbances in the serum protein pattern, particularly involving albumin and α_2-globulin, occur at a stage in the development of diabetic vascular lesions when the changes could not be accounted for by loss of protein in urine.

Serum Cholesterol

The mean value of serum cholesterol in diabetic patients with nephropathy was found to be raised in comparison with the other groups of diabetic patients. Because of this hypercholesterolaemia, a metabolic defect affecting lipid metabolism would appear to play a part in the pathogenesis of diabetic vascular disease in general and diabetic retinopathy and nephropathy in particular. The associated severe atherosclerosis and the markedly increased glomerular lipid in hyaline fibrinoid lesions (as seen in the biopsy material) give further support to this view.

Serum Polysaccharides

Normal human serum contains a relatively high concentration of complex polysaccharides bound to protein. The source, composition, and function of these glycoprotein substances are poorly understood. It has been repeatedly demonstrated that their concentration, and in some cases their composition, is altered in a variety of diseases (West and Clarke, 1938; Shetlar *et al.*, 1949). Some published data, notably those of Jacobs (1949), indicate that the concentration of polysaccharides measured as glucosamine is raised in the

serum of diabetic patients. Other figures suggest that diabetic patients have normal serum polysaccharides (West and Clarke, 1938 ; Shetlar *et al.*, 1949). The data in these studies were presented in such a way that the results could not be correlated with the absence or presence of vascular disease.

In order to explore the possibility of an association between a disturbance of polysaccharide metabolism and the occurrence of vascular disease in diabetic subjects, we have studied the serum polysaccharide levels in several groups of subjects. One group consisted of healthy male volunteers ; the others were diabetic patients. All cases in this study were free from other diseases, such as cancer, acute or chronic infections, and myocardial infarction, all of which are known to be associated with raised serum polysaccharide.

Serum polysaccharides were measured as galactose-mannose by the method described by Graff *et al.* (1951). From the data already recorded it is evident that the concentration of polysaccharides bound to serum proteins is significantly raised in diabetic patients, but this does not occur in association with the primary metabolic defect, but only in cases with well-established clinically detectable degenerative vascular disease. However, raised values were found in diabetic patients independent of the existence of abnormalities in renal function, as assessed by conventional clinical and laboratory methods. Increased values in the serum polysaccharides, which have been produced experimentally and which occur spontaneously in disease, are currently interpreted as a non-specific response to tissue injury, and in particular to alteration of connective-tissue polysaccharides (Berkman, 1955). Changes in subintimal mucopolysaccharide-ground substance have been implicated in the pathogenesis of arteriosclerosis, a local increase in the subendothelial mucopolysaccharides being an early feature and preceding lipoid deposition in the vessel wall (Altshuler and Angevine, 1951 ; Moon and Rinehart, 1952 ; Taylor, 1953). It is quite possible that the results obtained simply reflect widespread degenerative vascular disease in the diabetic patients selected for study, the elevated serum polysaccharide levels being the result of concomitant tissue injury. On the other hand, the facts still allow speculation about the possibility of a relation existing between the increased circulating polysaccharide and the eventual development of deposits of hyaline material of a mucopolysaccharide nature around certain capillaries in such patients. Indeed, we believe that the disturbance in the polysaccharide metabolism is related to the development of some of the pathological lesions in the kidney

Serum Electrolytes

The serum electrolytes have not been studied before in diabetes (except in ketosis and coma). The present study showed a normal serum sodium level in all groups of diabetics except those with diabetic nephropathy, who showed a low level (mean 131.5 mEq/l.), and especially those with oedema (mean 129 mEq/l.). This finding may appear at first glance contradictory to what is known about the pathogenesis of oedema, in which sodium retention is a prime factor. However, despite the lowered serum sodium level, the total body sodium must be much raised, because an approximate reduction of 7% of the plasma sodium concentration is more than outweighed by an increase of 100–200% in the extracellular fluid volume (plasma and interstitial fluid) containing this concentration of sodium (Prentice *et al.*, 1951 ; Warner *et al.*, 1952).

Treatment with low sodium diets and diuretics is instituted so commonly and intensively in nephrotic patients before they are hospitalized and their electrolytes studied, that it is difficult to be certain whether, or to what extent, altered serum electrolyte patterns are due to the nephropathy or are the result of treatment. Lastly, we do not yet know anything about the intracellular electrolyte changes in diabetic nephropathy. It may be quite possible that there is an increase in intracellular water and sodium and a diminution in intracellular potassium, similar to that which occurs in cases of congestive heart failure (Friedberg, 1956).

The serum potassium was lower in the uncomplicated diabetic patients, possibly owing to polyurea, and especially so in patients recovering from ketosis. In the patients with degenerative complications other than nephropathy the serum potassium was normal. In patients with diabetic nephropathy hyperkalaemia was a notable feature. This hyperkalaemia can be explained in part by the renal failure. The highest figures for serum potassium were found in patients with clinically manifest uraemic symptoms, and can be correlated with the levels of blood urea and the results of the urea-clearance test. This effect will become more evident if a shift of potassium from the intracellular to the extracellular compartment (as postulated above) is proved to be true.

Urinary Excretion of Corticoid Substances

Study of the urinary excretion of 17-hydroxy-corticosteroids (the end-product of glucocorticoids) has given important results in the diabetic cases studied. Diabetics with retinopathy, and especially those with nephropathy, have shown a marked rise in the excretion of this substance. Increased glucocorticoid activity in those groups of diabetic patients can therefore be assumed. When the figures are seen in relation to the diminished renal function in cases of nephropathy, the substantial rise of the serum glucocorticoids in these cases is still more marked.

The urinary excretion of 17-hydroxycorticosteroids in diabetics has been studied by many authors. Most of them reported a normal excretion of these hormones (Talbot *et al.*, 1947 ; Venning and Browne, 1947 ; Shadaksharappa *et al.*, 1951 ; Perkoff *et al.*, 1954). In these reports there was no attempt to study diabetic patients in separate groups. Maengwyn-Davies *et al.* (1956), however, have studied the urinary excretion of 17-hydroxycorticoid patterns in diabetic patients with and without diabetic retinopathy, and have shown a marked rise in its excretion in the latter group of patients. In our study, also, an important finding was excessive 17-hydroxycorticosteroid urinary excretion in patients with diabetic acidosis. Similar excessive glucocorticoid activity was reported by McArthur *et al.* (1950), Stowers (1951), and Perkoff *et al.* (1954).

Vitamin B_{12} Retention Test

We have shown that diabetic patients with no complications retain more of a test dose of vitamin B_{12} given parenterally than normal subjects do. This probably denotes a deficiency of this vitamin—as of other B vitamins—in diabetics, because of the amounts lost through the polyuria. Diabetics in episodes of

acidosis excrete a great part of the test dose of vitamin B_{12} given. Similarly, diabetics with hyaline fibrinoid lesions excrete the greater part of the test dose.

The interrelationship of vitamin B_{12}, diabetes, and adrenal cortical hormones has been explored (Becker *et al.*, 1953). Animals deficient in vitamin B_{12} were reported to exhibit hyperglycaemia (Ling and Chow, 1953). Vitamin B_{12} has been shown to abolish the hyperglycaemia in rats induced by large doses of glucose or by cortisone (Binkley *et al.*, 1951), and in humans it was shown to increase the insulin sensitivity and to antagonize the hyperglycaemic effect of prednisone in normal people and in diabetics (Darwish and Fikry, 1958). Furthermore, the administration of vitamin B_{12} labelled with radioactive cobalt-60 resulted in a relatively high concentration of radioactivity in the pancreas, kidneys, and adrenals of experimental rats. Cortisone administration increased the turnover of vitamin B_{12} in all organs studied, and resulted in a greatly increased excretion of vitamin B_{12} in the urine (Becker *et al.*, 1953). Similarly, in rats, vitamin B_{12} has been demonstrated to counteract such cortisone effects as thymus atrophy, alopecia, and inhibition of growth. It is therefore evident that vitamin B_{12} metabolism is intimately related both to the diabetic state and to the function of the adrenal cortex.

Becker *et al.* (1953) concluded that the decreased excretion of a test dose of vitamin B_{12} by diabetic patients is consistent with a deficiency, or abnormal retention, of this vitamin associated with the diabetic state. The increased excretion of a test dose of vitamin B_{12} by diabetics with retinopathy is related to the development of this degenerative complication.

We found in our groups of patients that if the diabetics with no degenerative complications were compared with those with degenerative complications, no difference in the result of the vitamin B_{12} retention test could be arrived at. But, by separating in the first group the cases with ketosis from those without it, and by subdividing the cases in the second group according to the presence or absence of hyaline fibrinoid lesions (ascertained by histological examination of material obtained by renal biopsy) we arrived at the following results: (1) The average normal excretion of vitamin B_{12} in the eight-hour urine specimen after 100 μg of vitamin B_{12} intramuscularly was 18 μg. (2) Diabetics without degenerative lesions and without ketosis retained most of the test dose; they excreted an average of 6.1 μg. (3) Diabetics without degenerative complications but with ketosis could not retain as much as did those with no ketosis: they excreted an average of 41 μg. (4) Diabetics with nephropathy and hyaline fibrinoid lesions excreted most of the test dose—an average of 70 μg. (5) Diabetics with nephropathy but with no hyaline fibrinoid lesions showed normal vitamin B_{12} excretion—21.5 μg.

It seems possible, therefore, that Field *et al.* (1957) could not establish any relationship between the results of the vitamin B_{12} retention test and the degenerative complications of diabetes because they included cases with ketosis in the group showing no degenerative complications, and because they studied all the degenerative complications together, not distinguishing the group with hyaline fibrinoid lesions from the rest of the diabetics with degenerative complications.

The findings that diabetics with ketosis and hyaline fibrinoid lesions cannot retain vitamin B_{12} is indirect evidence of excessive glucocorticoid function in these patients. Experimental chronic alloxan diabetes in rats was noted to induce vitamin B_{12} deficiency and cause excessive retention of a test dose of this vitamin. Cortisone administered to rats was found to mobilize vitamin B_{12} from all tissues and increase its excretion in the urine (Becker *et al.*, 1953). This occurred even in the presence of a marked vitamin B_{12} deficiency, thus aggravating the deficiency state (Wahlstrom and Johnson, 1951). When testosterone was administered to diabetics with retinopathy a marked reduction in the excretion of the test dose of vitamin B_{12} resulted, approaching the excretion level in those without retinopathy (Becker *et al.*, 1953).

Diabetics with acidosis and with nephropathy show the highest urinary values of 17-hydroxycorticoids. The same group also show the minimum retention of a test dose of vitamin B_{12}. Excess glucocorticoid function is therefore the probable cause of the inability of the diabetic patient to retain vitamin B_{12}, even though an actual state of deficiency exists.

Pathogenic Relationship of Metabolic and Endocrine Disturbances to Development of the Lesions of Diabetic Nephropathy

Serum Mucopolysaccharides

Since McManus (1950b) suggested that the source of the hyaline material of nodular glomerulosclerosis might be an abnormal circulating polysaccharide (because of the mucopolysaccharide nature of this hyaline material) many workers began to study the level of the serum polysaccharides and to correlate it with the development of diabetic glomerulosclerosis and diabetic nephropathy.

We know very little about the basic physiology and metabolism of ground substance, and the interpretation of changes in the levels of serum mucopolysaccharides is fraught with great difficulty. But evidence is accumulating which points to a metabolic disturbance in this substance as a primary defect responsible for the pathogenesis of the hyaline retinal and glomerular lesions in diabetes.

First, the serum mucopolysaccharides are largely bound to the α_2-globulin fraction of the serum proteins in man (Gilliland *et al.*, 1954). A decrease in the serum albumin and α_1-globulin and a significant increase in α_2-globulin were found in diabetic patients long before any proteinuria was present. This can be taken as indirect evidence of the raised serum mucopolysaccharides at this stage in the disease.

Secondly, Berkman *et al.* (1954) have studied the serum polysaccharides in two groups with arteriosclerosis—the first group diabetic and the second non-diabetic patients. In contrast to the pattern in diabetic patients, the values for total polysaccharides and for serum glucosamine were normal or very slightly elevated in the majority of non-diabetics.

Thirdly, the observation of McManus (1950a) that the hyaline material of glomerulosclerosis is not deposited in ischaemic glomeruli indicates that it probably originates from circulating serum polysaccharides.

Lastly, the fact that all observers, including ourselves, have reported very high values for the serum polysaccharides in diabetic retinopathy and diabetic nephropathy—values much higher than in any other generalized degenerative vascular disease—may be seen to be related to the finding that these specific diabetic

capillary lesions contain the largest known deposits of this hyaline material.

Serum Lipoproteins

Another aspect of disordered metabolism of the diabetic has been illuminated by the observations of Engelberg *et al.* (1952b) and by Keiding *et al.* (1952) on serum lipoproteins. These workers noted a marked increase in the S_f 12-20 class of circulating lipoproteins in diabetic patients with retinopathy and nephropathy. Simon (1940) first stressed the lipohyaline nature of the deposits in glomerulosclerosis. Wilens *et al.* (1951), in an extensive study of glomerular fat, demonstrated the inordinately high lipid content of the glomerular nodules and drew attention to the possibility that a fatty deposit was one of the initial occurrences in the development of these pathological defects. Now, by the histochemical examination of renal biopsy material, we have found that the nodular lesions are devoid of fat, but that the hyaline fibrinoid lesions are probably a lipoprotein (Sabour *et al.*, 1959). Thus an equally attractive argument can be postulated for a disturbed metabolism of lipoproteins as for mucoids, the latter being responsible for the development of diffuse and nodular glomerulosclerosis and the former for the development of the hyaline fibrinoid renal lesions.

However, it should be noted that other diseases with raised serum lipoproteins, such as myxoedema, nephrosis, and atherosclerosis, do not show the specific fibrinoid lesions of diabetes. This can be accounted for by the fact that these hyaline fibrinoid lesions were found only in glomeruli which were already the seat of glomerulosclerosis, nodular or diffuse. This probably shows that a local mechanical factor is necessary to provoke the onset of these lesions in the presence of a high lipoprotein content of the plasma.

Adrenocortical Function

We have found a significantly increased excretion of glucocorticoids in patients with diabetic nephropathy. Similar results had been previously obtained in cases with diabetic retinopathy. The Thorn test showed that patients with diabetic nephropathy develop a more marked eosinopenia four hours after 25 units of corticotrophin than diabetics without nephropathy. These findings point to a possible role of increased glucocorticoid activity in the pathogenesis of diabetic nephropathy. Moreover, the following observations provide additional evidence of the importance of the adrenal cortex in the pathogenesis of the retinopathy–nephropathy syndrome in diabetics.

A: Suggestive Clinical Observations.—(1) Diabetic retinopathy has appeared for the first time in non-hypertensive diabetics during pregnancy, and cleared completely after delivery (Lawrence, 1948; Becker, 1952). (2) Many diabetics with retinopathy have been observed whose ocular disease showed startling progression during the last trimester of pregnancy and subsequent post-partum regression (Becker, Maengwyn-Davies *et al.*, 1954). (3) Berkman *et al.* (1953) have noted an increase of the urinary signs of diabetic nephropathy after the administration of corticotrophin. (4) Retinal capillary aneurysms have been observed clinically to appear in non-diabetic patients during intravenous corticotrophin therapy and to disappear when treatment ceased (Becker, Maengwyn-Davies *et al.*, 1954).

B: Therapeutic Reports.—Mechanisms that decrease the activity of the adrenal cortex have occasionally been seen to improve diabetic retinopathy (and nephropathy). Thus hypophysectomy (Kinsell *et al.*, 1954), bilateral adrenalectomy (Green *et al.*, 1950; Wortham and Headstream, 1954), and administration of D.D.D. (Törnblom, 1956) were all reported to have this effect and to correct the disturbed chemistry in patients with diabetic retinopathy and nephropathy.

C: Histopathological Data.—Becker (1952) stated that "diabetics with retinopathy and K.W. disease, in contrast to uncomplicated diabetes, had heavier adrenals with excessive lipoid vacuolization of the zona fasciculata, and an abnormally high incidence of adrenal cortical adenomata."

D: Experimental Evidence.—Glomerular lesions identical with the hyaline fibrinoid lesions can be produced in rabbits by the administration of cortisone (Rich *et al.*, 1950). When cortisone or corticotrophin was administered to alloxan-diabetic rabbits, the incidence of the renal lesions and the retinal capillary aneurysms increased (Becker, 1952).

From the above data it is apparent that increased adrenal cortical activity is involved in the pathogenesis of diabetic retinopathy and diabetic nephropathy. It is of interest to note that cortisone administration to rabbits results in marked lipaemia (Rich *et al.*, 1951; Cook *et al.*, 1952), with elevation of the lipoprotein component in the S_f 10-30 class. Alloxan-diabetic animals are more susceptible to lipaemia, and alloxan diabetes blocks the conversion of lipoproteins of the S_f 80-100 class into lipoproteins of a lower S_f class. Thus, alloxan diabetes and cortisone, which act together to produce renal lesions in the rabbit (Wilens and Stumpf, 1955; Bloodworth and Hamwi, 1956), also behave similarly in interference with lipoprotein metabolism. The experimental lesion produced by cortisone administration to alloxan-diabetic rabbits is not identical with K.W. hyaline nodules, but with the hyaline fibrinoid lesions (Le Compte, 1957). Thus since an alteration in lipoprotein metabolism is involved in the pathogenesis of the hyaline fibrinoid lesions, and since changes in adrenal cortical activity are associated with alterations in the serum lipoproteins, the abnormal levels of serum lipoproteins reported in the nephropathy group of diabetic patients are entirely consistent with the hypothesis that the adrenal cortex plays a part in the development of these lesions.

Vitamin B_{12}

Excess glucocorticoids have been shown to cause excessive excretion of vitamin B_{12} in animals (Wahlstrom and Johnson, 1951), in humans treated by cortisone (Becker, Allen, *et al.*, 1954), and in diabetics with acidosis or with hyaline fibrinoid lesions. Diabetics are themselves deficient in vitamin B_{12}, as they are in other B vitamins, and hence retain most of the test dose given. Hyperfunction of the suprarenal gland, when it occurs, will prevent the diabetics from retaining the vitamin B_{12} and thus will exaggerate the deficiency state.

By performing the vitamin B_{12} excretion test and examining renal biopsy specimens, we have shown that excessive excretion of vitamin B_{12} does not occur in all cases of diabetic nephropathy. It did occur in cases in which there were hyaline fibrinoid renal lesions, but not in cases with diffuse or nodular glomerulosclerosis, no matter how advanced such lesions were. Therefore this metabolic defect is shown to be related to the development of the hyaline fibrinoid lesions and not to the other renal lesions.

Summary

Sixty-five diabetic patients were investigated to elucidate the endocrine and metabolic defects associated

with diabetic nephropathy and to demonstrate by needle biopsy studies the pathogenic relationship of these defects to the development of the renal lesions.

Cases of diabetic nephropathy showed hypoalbuminaemia, hyperglobulinaemia, hypercholesterolaemia in many instances, a rise in the protein-bound serum polysaccharides, hyponatraemia, and hyperkalaemia. The urine showed excessive amounts of 17-hydroxycorticosteroids and low values of 17-ketosteroids. Most patients with diabetic nephropathy could not retain the greater part of a test-dose of vitamin B_{12} administered parenterally.

The following endocrine and metabolic disturbances are believed to be probably responsible for the development of the renal lesions: a disturbance in protein metabolism resulting in a rise in α_2 and β-globulins: a disturbance in lipid metabolism causing lipaemia and especially a rise in the smaller aggregates of the serum lipoproteins; a disturbance in carbohydrate metabolism leading to a rise in the serum polysaccharide; excessive glucocorticoid activity; and inability to retain vitamin B_{12}.

The high serum mucopolysaccharides are probably related to the development of the lesions of diffuse and nodular glomerulosclerosis. The disturbed lipoprotein metabolism, vitamin B_{12} metabolism, and the excessive glucocorticoid activity are probably related to the development of the hyaline fibrinoid lesions.

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MITRAL VALVOTOMY AND RESTENOSIS

BY

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The occurrence of restenosis after an adequate mitral valvotomy has been questioned, but reports in the literature of well-documented cases imply that it does undoubtedly occur (Jordan and Hellems, 1952; Keyes and Lam, 1954 Donzelot; *et al.*, 1953; Santy *et al.*, 1954; McKusick, 1955; Glenn and Dineen, 1956). However, the true incidence of restenosis is not known.

In many patients apparent restenosis has been attributed to inadequate initial valvotomy. Thus Harken and Black (1955) have declared that restenosis is most uncommon. Glover *et al.* (1955) have seen no case of restenosis following valvotomy in their series. From their experience in a review of 250 cases subjected to mitral valvotomy followed from one to six years, Turner and Fraser (1956) felt that refusion of the commissures must be very rare. Of their cases five had second valvotomies and three more were under consideration at the time of writing. It was the opinion of the surgeon that in no case had refusion occurred, but that the original split had been inadequate.

On the other hand, Belcher (1958) described 12 cases in which revalvotomies were undertaken, and drew a

distinction between "true" and "false" restenosis. True restenosis occurred after one or both commissures had been fully split. Four cases fell into this group. In false restenosis either an original split was not obtained or there was no split beyond the area of insertion of the papillary muscles: there were eight cases of this type. Baker *et al.* (1955) found that three years after mitral valvotomy 10% of patients had lost all improvement gained by the operation. However, these were all severe cases operated upon early in their series. Wood (1954) reported an incidence of restenosis of 5% during the first three-year follow-up period after mitral valvotomy. Likoff and Uricchio (1958), reviewing the clinical status of 200 patients five to eight years after operation, found restenosis in 5% also. In the analysis by Bailey *et al.* (1957) of 1,000 cases following mitral valvotomy, restenosis had occurred in 22. In six there was necropsy evidence to support this, and further operations in the other 16 showed that restenosis had occurred. Soulié *et al.* (1957) report six cases of restenosis verified at second valvotomies.

It is the purpose of this paper to report 15 cases in which there was a recurrence of symptoms following mitral valvotomy. In seven restenosis of the mitral valve occurred after a satisfactory valvotomy. In the other eight the initial valvotomy was inadequate. Twelve of these patients have had second valvotomies and the other three are awaiting operation.

In addition to these 15 patients one further case of restenosis seen at necropsy is recorded.

The Patients

In general the 15 patients followed a similar clinical course. At the time of the first valvotomy they all presented the signs of critical mitral stenosis. There was an initial period of improvement after operation, with subsequent deterioration. The average duration of improvement in those who had had an apparently satisfactory valvotomy was three years, whereas it was two and a half years for those in whom the initial valvotomy was poor (Fig. 1). Gradual deterioration ensued in all patients from one to five years after the initial valvotomy. At the time of the second operation, or at the time of assessment of those awaiting second valvotomy, the incapacity caused by exertional dyspnoea was more severe than it had been prior to the first operation, with two exceptions (Table I). Coinciding with the period of improvement in the seven patients who had better valvotomies there was a diminution in the signs of mitral stenosis, in that the mitral diastolic murmur became shorter or softer, or even inaudible. At the time of assessment prior to the second valvotomy all again presented the signs of critical mitral stenosis.

Associated Valve Lesions. — In these patients associated valve lesions or mitral incompetence were not considered to have contributed in any material way to the worsening of their symptoms and signs. In fact, in eight no other lesion was present. In five patients faint early diastolic murmurs were heard. There were no peripheral signs of aortic incompetence. In two slight mitral incompetence was produced at the first operation. Minimal left ventricular hypertrophy on the electrocardiogram was present in two.

Radiology.—Prior to the second operation there had been a deterioration in the radiological signs since the time of the first valvotomy in 11 patients. This was judged by an increase in heart size, the appearance of horizontal costophrenic lines, and an increase in the radiological signs of pulmonary arterial hypertension.

Electrocardiography.—In five patients the degree of right ventricular hypertrophy had increased between the two valvotomies. But in six patients a definite but transient diminution in the degree of right ventricular hypertrophy did occur after the first operation. The changes, however, were slight (Fig. 2).

Cardiac Catheterization.—Of the 15 patients, 11 were catheterized before the second operation. All pressures were measured from 5 cm. below the sternal angle. In nine the mean pulmonary capillary pressure was recorded. The readings obtained were within the range of 20 to 35 mm. Hg with the

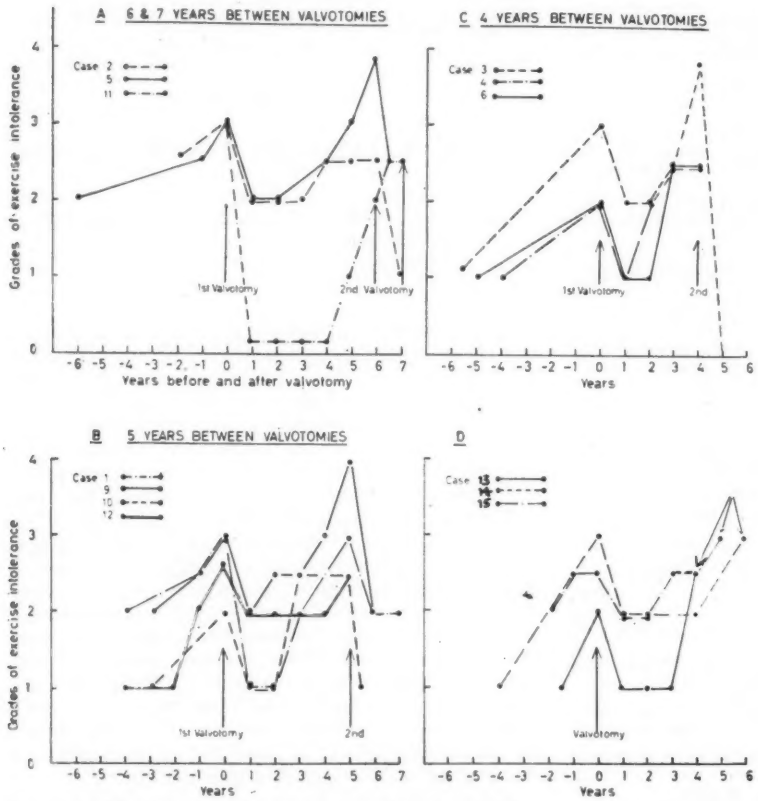

FIG. 1.—Level of exercise intolerance in relation to each valvotomy. Cases 7 and 8 are excluded.

TABLE I.—*Clinical Data*

Case No.	Age at 1st Valvotomy	Exercise Intolerance*		Clinical Signs		Years of Improvement Following 1st Valvotomy
		Before 1st Valvotomy	Before 2nd Valvotomy	Before 1st Valvotomy	Before 2nd Valvotomy	
1	45	3	3	Pure M.S. Mobile valve	Pure tight M.S. Mobile valve	4
2	27	3	2B	Pure tight M.S. Mobile valve	,, ,,	3
3	38	3	4	Pure tight M.S. Severe P.H.T. Mobile valve	Pure tight M.S. Severe P.H.T. Mobile valve	2
4	39	2A	2B	Pure tight M.S. Mobile valve	Pure tight M.S. Mobile valve	1
5	43	3	4	Pure tight M.S.	Pure tight M.S. Severe P.H.T. P.I.	4
6	40	2A	2B	Pure tight M.S. Mobile valve	Tight M.S. Slight M.I. Mobile valve	2
7	18	2A	1	Pure tight M.S. Mobile valve. P.H.T.	Pure tight M.S. Mobile valve. P.H.T. ++	2
8	50	2B	2B	Pure tight M.S. P.H.T.	Pure tight M.S. P.H.T.	1
9	32	3	4	Pure tight M.S. Mobile valve. P.H.T.	Pure tight M.S. Mobile valve. P.H.T.	1
10	37	2A	2B	Pure tight M.S. Mobile valve	Pure tight M.S. Mobile valve. P.H.T. +	2
11	36	3	2B	Pure M.S. Mobile valve	Pure M.S. Mobile valve	4
12	40	2B	2B	,, ,,	,, ,,	4
13	46	2A	3	Pure tight M.S.	Pure tight M.S. Rigid valve	3
14	47	3	3	,, ,,	Tight M.S. Slight M.I.	5
15	31	2B	2B	Tight M.S. ? Some M.I.	Tight M.S. ? Some M.I.	2

Restenosis patients, Cases 8–14.
* Exercise intolerance: grades 0–4 according to the classification of the American Heart Association. M.I.=Mitral incompetence. P.H.T.=Pulmonary hypertension. M.S.=Mitral stenosis. P.I.=Pulmonary incompetence.

exception of one which was 16 mm. Hg (Table II). The pulmonary wedge or left atrial pressure had been measured before the first operation in three, and in each case the pressure was higher at the later assessment. The pulmonary artery pressure was measured prior to the second operation in 11 cases. The pressure before the second operation was much higher than before the first in four of five patients in whom a reading immediately preceding the first operation had been obtained, and there was an increase in total pulmonary resistance during the interval period (Table II).

Findings at Valvotomy.—In two cases no actual fracture of a commissure was achieved at the first operation, and in another five, though the valve was split, the increase in size was small and the differences found at the second operation were not great. In the other five patients who had a second operation the valves had been split reasonably well on the first occasion, the average size of the orifice produced being 3 cm. in diameter. The average orifice diameter found at the second operation was 1.1 cm. Likewise, in the three cases awaiting second valvotomies definite valve splits had previously been obtained. In one the split was poor, but in the other two 3-cm. and 3.5-cm. valves were produced (Table III).

Pathology.—Biopsies were taken from the left atrial appendage in 11 patients at the first operation. Aschoff bodies were present in three, and were considered by Professor C. V. Harrison to show evidence of active rheumatism. Two of these patients had good initial valvotomies.

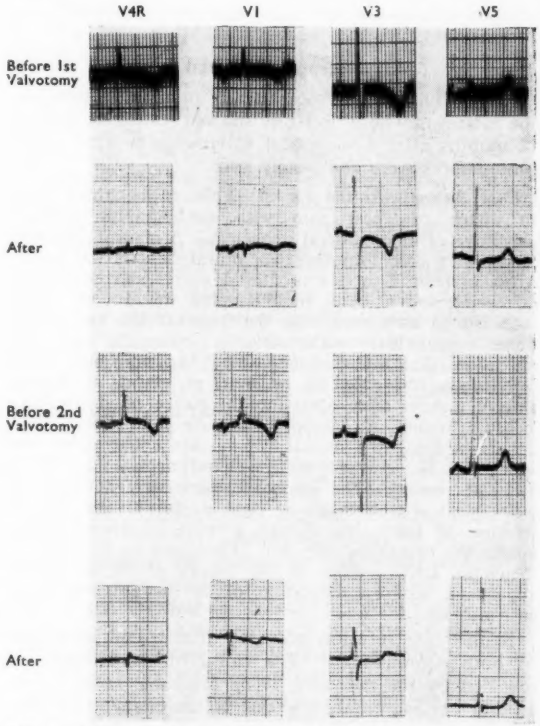

FIG. 2.—Case 3. Electrocardiogram in relation to valvotomies. The dominant R in lead V, disappeared after the first valvotomy and reappeared coinciding with a return of symptoms. It disappeared again after the second valvotomy.

TABLE II.—*Catheter Data*

Case No.	Prior to 1st Valvotomy						Between Valvotomies					
	Date of Cardiac Catheter	Pressures mm./Hg P.A. or R.V.	Pressures mm./Hg P.C.P.	Cardiac Output (l./min.)	Total Pulmonary Resistance (Units)	Date of Operation	Date of Cardiac Catheter	Pressures mm./Hg P.A. or R.V.	Pressures mm./Hg P.C.P.	Cardiac Output (l./min.)	Total Pulmonary Resistance (Units)	Date of Operation
1	1/1/51	67/2 (R.V.)		3·6		7/3/51	23/3/56	70/35	32	6·0	7·0	4/4/56
2	29/1/51	36/19		5·4	3·7	9/4/52	6/5/57	41/21	23	6·0	3·8	17/5/57
3	17/1/52	128/67				6/2/52	14/8/56	78/10 (R.V.)		2·7		18/8/56
4						13/1/54	28/5/58	40/17	16	4·6	4·0	30/5/58
5						10/2/52						5/9/58
6						6/5/52	15/10/56	45/15	26	4·6	3·9	6/11/58
7						20/1/54	18/1/57	65/45	25	6·0	5·8	10/4/57
8						4/8/54	15/3/57	79/48		1·7	31	18/10/57
9	27/10/50	78/18 (R.V.)		3·2		30/5/51	18/4/52	56/38		2·3	17	12/9/56
10	29/4/53	34/19		4·5	4·2	29/4/53	6/2/58	100/60	35	3·5	19	13/8/58
11						16/1/52						16/3/59
12	18/2/53	46/27		4·7	6	12/3/54						29/1/59
13	28/4/54	35/14	16	8·1	2	22/9/54	12/1/59	62/30	20	4·4	8·2	
14			20 at operation			10/9/52	1/12/58	74/37	34	5	8·8	
15	5/1/53	38/21	22	5·3	4	29/9/54	14/1/59	75/43	30	8·5	6·0	

Restenosis patients, Cases 8–14. P.A.=Pulmonary artery. R.V.=Right ventricle. P.C.P.=Pulmonary capillary pressure.

TABLE III.—*Operation Data*

Case No.	1st Valvotomy					2nd Valvotomy				
	Valve Size	Calcium	Mobility	Commissure(s) Split	Final Valve Size	Valve Size	Calcium	Mobility	Commissure(s) Split	Final Valve Size
1	1 cm.	0	Both cusps	0	2 cm.	1 cm.	0	Both cusps	Both	3 cm.
2	1 ,,	0	,, ,,	0	2 ,,	1 ,,	0	,, ,,	Lateral	3·5 ,,
3	0·8 ,,	0	Ant. cusp	Lateral	1·75 ,,	0·8 ,,	0	Ant. cusp	Both	4 ,,
4	1·2 ,,	0	,, ,,	,,	2·5 ,,	1·8 ,,	0	,, ,,	,,	3 ,,
5	1 ,,	0	Both cusps	,,	2·5 ,,	0·8 ,,	0	Both cusps	,,	4 ,,
6	1·5 ,,	0	,, ,,	,,	3 ,,	1·5 ,,	0	Ant. cusp	,,	3·4 ,,
7	1 ,,	0	,, ,,	,,	2 ,,	0·8 ,,	0	Both cusps	Aortic cusp torn	3 ,,
8	0·8 ,,	+	Ant. cusp	,,	2·5 ,,	1·5 ,,	++	Almost immobile	Both	4 ,,
9	1·2 ,,	0	Both cusps	,,	3 ,,	1 ,,	0	Both cusps	Lat. part of medial	3·5 ,,
10	0·9 ,,	+	Ant. cusp	,,	3 ,,	1 ,,	+	Ant. cusp	Both	3·5 ,,
11	0·7 ,,	0	Both cusps	Medial; ½ lateral	3 ,,	1·25 ,,	0	Both cusps	,,	3·5 ,,
12	1·5 ,,	0	,, ,,	Lateral	3 ,,	1 ,,	0	,, ,,	Lateral	3 ,,
13	1·5 ,,	+	Partially mobile	,,	3·5 ,,					
14	0·8 ,,	+	Not stated	,,	3 ,,					
15	1·5 ,,	0	Fair	Partial, lateral	2·5 ,,					

Necropsy Material

In addition to the cases already presented there was one patient in whom necropsy showed restenosis present 12 months after a successful valvotomy in which both commissures were completely split.

Case Report.—At the age of 37 the patient (M.Y.) had an attack of chest pain with cardiographic changes suggestive of antero-lateral ischaemia. A clinical diagnosis of coronary embolism and tight mitral stenosis was made. After an interval of six months a mitral valvotomy was performed and a 1-cm. mobile valve was found. Both commissures were split with the finger to the valve ring. There was no subvalvular stenosis. After the operation the mitral diastolic murmur, which had previously been full length, was noted to be short on several occasions. Twelve months after operation the patient died suddenly in bed at home. At necropsy a definite line of refusion of the cusps along the medial commissure could clearly be seen (Fig. 3). An old postero-lateral myocardial infarct was also present. The coronary vessels were healthy. A histological section taken at right angles to the line of refusion of the valve showed a mass of fibrous tissue joining the two cusps (Fig. 3*c*). There was no evidence of rheumatic activity either in the biopsy of the left atrial appendage taken at operation or in the sections taken post mortem.

In this case refusion occurred after a complete split of both commissures. The cause of death was not revealed by the necropsy. The evidence, however, of an old cardiac infarction due to coronary embolism suggests that it may have been due to arrhythmia.

Discussion

There is little doubt that in 7 of the 15 patients considerable restenosis occurred. In six of these a complete split of the lateral commissure was achieved at the first operation, and in the seventh the medial commissure was split to the valve ring and the lateral commissure was partially split also. In no case was subvalvular stenosis found. Symptomatic improvement followed in all. In each the mitral diastolic murmur became shorter or softer, and in three the degree of right ventricular hypertrophy seen on the electrocardiogram became temporarily less. In the five patients of this group who have had second valvotomies (Cases 8–12) definite proof of restenosis was provided by comparing the valve size found at the second operation with the orifice size known to have been produced at the first (Table III). Thus the average valve diameter produced at the first operation in this group was 3 cm., while the average size of the valve orifice found at the second operation was 1.1 cm. At the time of maximum deterioration immediately preceding the second valvotomy the signs of critical mitral stenosis were again present. The electrocardiographic and radiological changes were as marked as they had previously been or were more severe (Table I), and the pulmonary artery pressure, where measured, had risen in all except one case.

Baden (1958) refers to restenosis occurring after only one commissure has been split as "false" restenosis and accepts as examples of "true" restenosis only those cases in which restenosis has occurred after a complete splitting of both commissures. However, it would seem that if one commissure is completely split and the chordae tendineae are freed and then refusion occurs, this is as "true" a restenosis as if both are split and then re-fuse. Also, even though the first valvotomies were poor in the other eight patients there is evidence that structural changes occurred in the valves between valvotomies to convert a partially relieved obstruction to a critical stenosis again (Table III). Hence some restenosis may fairly be said to have occurred.

Few well-authenticated cases have been reported in which restenosis has occurred in a mobile valve following a complete split of both commissures and separation of fused chordae, as in case M. Y. In neither this case nor that of Baden (1958) was there any evidence of rheumatic activity. In the case reported by Harken and Black (1955) thrombus had formed between the valve edges producing a recurrence of a part of the original stenosis. In two further cases they attribute restenosis to traumatic endocarditis produced by blunt dissection. In McKusick's (1955) case there was good evidence of continuing rheumatic activity.

Bailey *et al.* (1957) have suggested that restenosis is related to the mobility of the valve and that fibrin and platelet deposition on the valve as demonstrated by Magarey (1951) is more likely to occur if the valve leaflets are moving sluggishly. Brock (1952) implied a similar mechanism if the movement of the valve cusps is not restored by division and separation of the critical areas of tendon insertion. Nevertheless, he felt that if the lateral commissure only was completely split and the corresponding area of tendon insertion freed, mobility of the valve would be restored and recurrence was unlikely. Glover *et al.* (1955) and Harken and Black (1955) also expressed this view.

In the cases described in this paper in which restenosis occurred after a seemingly adequate valvotomy there is no good evidence that restenosis and lack of mobility of the valve leaflets ran parallel. The mobility of both

cusps was described as good in three cases at the time of the first valvotomy; only the anterior cusp moved in a further 3, and the mobility is not recorded in the other (Table III). In the necropsy case (M. Y.) both cusps were freely mobile. These findings correlated well with the clinical estimate of valve mobility based on the loudness of the first heart sound in the mitral area and the presence and intensity of the opening snap. In four of these seven patients some valve calcium was found; no macroscopic calcium was present in the necropsy case. Thus calcium was present in 50%, as compared with 33% in the series of 93 patients followed from five to seven years after valvotomy. The incidence, therefore, was slightly higher in the restenosis cases, but the numbers are small.

Persistent rheumatic activity did not appear to be a likely factor in the pathogenesis of restenosis in these patients. In no case was there a definite further attack of rheumatic fever. Aschoff bodies were found in the left atrial biopsy in two patients at the first operation. In one of these (Case 11) gradual deterioration followed an attack of mild joint pains lasting several weeks. There was no clinical evidence of rheumatic activity as indicated by normal erythrocyte sedimentation rate, normal temperature, and anti-streptolysin titre, but despite these results the episode may have been a manifestation of further rheumatic activity. McKeown (1953) has shown that the pathology of the left atrial biopsy is representative of the changes in the myocardium of the ventricle, yet discrepancy between the biopsy and the clinical findings has been the general rule. No correlation was found between the atrial biopsy and the subsequent clinical course by Baker *et al.* (1955) or by Goodwin *et al.* (1955). The same percentage of positive biopsies was found in the patients in whom restenosis occurred as in the whole series in Likoff and Uricchio's (1958) cases.

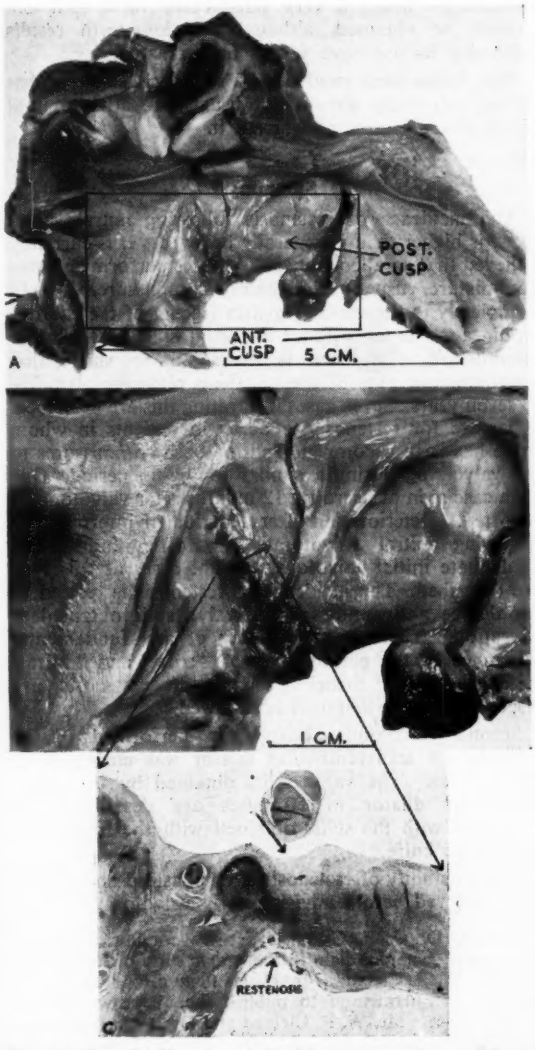

FIG. 3.—Case M. Y. *A* and *B:* Necropsy specimen of heart showing line of refusion of cusps along medial commissure. *C:* There is dense fibrous tissue joining the two cusps. (Haematoxylin and eosin. ×7,027.)

It is difficult to see how lack of valve mobility in these patients could explain the much higher incidence of restenosis seen after a complete split of one commissure, with or without a partial split of the other, compared with the incidence after a complete split of both commissures. Under these conditions restenosis is rare after a similar follow-up period, according to the literature. It is tempting to conjecture that this difference is purely a matter of time and that with a longer period of follow-up many more cases of restenosis appearing after complete splits of both commissures will emerge. This would seem inevitable if Magarey's (1951) view is correct that fibrin and platelet deposition on the valve surface with subsequent organization occurs as the initial stage in the development of restenosis.

Incidence of Restenosis

Any attempt to establish the incidence of restenosis must relate it to the extent and nature of the valve split previously obtained. At times it may be difficult for the surgeon to be precise on this point, and so the incidence must remain approximate. The seven patients with restenosis after a successful valvotomy were among 70 patients who had a satisfactory commissural split to produce a valve size of at least 2.5 cm. in diameter and who have been followed for five to seven years. They were taken from 93 who had valvotomies and who have been followed for a similar time. Of these, 10 died during the follow-up period and 13 had poor valvotomies and have been excluded. Thus there is an incidence of restenosis of 10% after five to seven years in the patients who had a successful valvotomy. The valve splits in the 70 patients were as follows:

Lateral commissure only	35
,, ,, and partial split of the medial commissure	19
Medial commissure only	3
,, ,, and partial split of the lateral commissure	4
Both commissures	9

There has so far been no evidence of restenosis in the cases above in which both commissures were divided as was seen in case M.Y. The incidence after a split of one commissure, usually the lateral with or without a partial split of the other, is therefore 11% after five to seven years. This is higher than was found by Likoff and Uricchio (1958), but roughly the same as Wood's (1956) figure of 2% per annum. However, neither figure was correlated with the extent and nature of the commissural splits. The incidence after a partial split of a commissure of a dilatation only of a valve is very much higher again. Eight of the 13 patients

who had poor valvotomies are described in this paper (Cases 1 to 7 and Case 15) and seven to date have had second valvotomies.

Method of Valvotomy

A dilator introduced through the wall of the left ventricle as described by Logan (1954, personal communication) was employed at the second valvotomy in 10 patients. In eight a splitting of both commissures was obtained and in one a split of the lateral commissure only. Unfortunately, in the other patient (Case 7) the aortic cusp was torn and gross mitral incompetence was produced. Nevertheless, it does seem that a more complete splitting of both commissures is possible with this instrument. In Table IV the valve splits obtained in the last 50 cases in which the transventricular dilator was employed are compared with those obtained in the last 61 cases in which the surgeon's finger was used with or without a valvotomy knife. These valvotomies were all performed later than December, 1954.

TABLE IV

	Using Transventricular Dilator	Using Finger and Valvotomy Knife
Lateral commissure only	11	31
,, ,, and partial split of the medial commissure	9	6
Medial commissure only	2	4
,, ,, and partial split of the lateral commissure	4	1
Both commissures	22	7
Partial split of both commissures	2	0
Poor or no split	0	12
Total	50	61

The efficacy of this method in obtaining a maximum valve split is apparent. Complete splits of both comissures were obtained in 44% with the transventricular dilator as compared with 11.4% using the finger and valvotomy knife, and 9.4% in the five to seven-year follow-up cases operated upon before December, 1954. The dilator produced torrential mitral incompetence in one patient (Case 7). If the incidence of severe mitral incompetence is shown not to be higher after this technique than after other methods it may well become the method of choice when it is not possible to split the valve satisfactorily with the finger alone.

Conclusions

Recurrence of symptoms following mitral valvotomy is often due to restenosis. It is probable that restenosis is much more common than hitherto supposed. The incidence of restenosis in the group in which one commissure only is split (usually the lateral), with or without a partial split of the other, is of the order of 11% after five to seven years. The incidence in the group in whom both commissures are split cannot be determined, but the literature suggests that it is rare after a similar follow-up period. The incidence after a partial split of one commissure or a dilatation only of a valve is very high—8 out of 13 cases. There is no evidence to suggest that there is any fundamental difference between the processes of "true" and "false" restenosis and there seems no reason to use these terms. If the valvotomy is poor there is a considerable chance of further obstruction developing. If the valvotomy is moderate then the chance of refusion occurring is less, whereas if it is excellent the chances are very slight for this follow-up period. It is unlikely that continuing or renewed rheumatic activity is commonly responsible for restenosis. Progressive organization of fibrin and platelet deposit on the opposing surfaces of the valve leaflets is the theory of the pathogenesis of restenosis which best fits the known facts. Restenosis may occur whether the valve is mobile or not.

It seems certain that in the near future a much greater number of second valvotomies will be performed. There are two reasons for this. First, many of the earlier valvotomies were inadequate and not even a complete split of one commissure was obtained. Second, the period of five to seven years has now elapsed since operations producing a complete split of one commissure were performed, and it can be expected that approximately 11% of those will restenose. Furthermore, even with the more modern techniques and greater experience it seems very probable that there will always be a number of patients in whom it is technically impossible to split completely more than one commissure at operation. The transventricular dilator provides a method by which a very satisfactory valve split can usually be obtained, although the long-term results following its use have yet to be evaluated.

The appreciable incidence of restenosis suggests that mitral valvotomy should not usually be advised until the patient's symptoms warrant it.

Summary

The incidence of restenosis following mitral valvotomy is higher than is generally believed. It is currently believed that an adequate valvotomy is performed if one commissure, usually the lateral commissure, is split completely to the valve ring with freeing of the chordae tendineae with or without a partial split of the other commissure. Evidence is presented to show that approximately 11% of these patients restenose after five to seven years. Seven cases illustrating this are described. It is rare for restenosis to occur in patients in whom there has been a complete split of both commissures to the valve ring during a similar follow-up period. One such case seen at necropsy 12 months after valvotomy is reported. Deterioration after a period of improvement following mitral valvotomy very often follows an inadequate initial valvotomy. Eight cases of this type are described. The incidence of restenosis is related to the degree and nature of the valve split obtained at operation. There is no evidence of any fundamental difference in the pathogenesis of "true" and "false" restenosis. The theories relating to restenosis are discussed and the literature is reviewed.

Second valvotomies have been performed on 12 patients. A transventricular dilator was employed in 10 of these. The valve splits obtained by the transventricular dilator in 50 cases are described and compared with the splits obtained with the finger and valvotomy knife.

The possibility of restenosis is emphasized and should be considered before advising early valvotomy.

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[ADDENDUM.—Since submitting this paper the three patients awaiting second valvotomy have had their operations and in each case the valve was tightly stenosed.]

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CALCIFIC MITRAL STENOSIS AND MITRAL VALVOTOMY

BY

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Approximately one-third of all patients submitted to surgery for the relief of mitral stenosis have calcium deposits on the valve leaflets (Sellors *et al.*, 1953 ; Wood, 1954 ; Goodwin *et al.*, 1955 ; Turner and Fraser, 1956 ; Bailey and Morse, 1957). Most authors stress the hazards of mitral valvotomy in the presence of heavy valve calcification. Calcific emboli may occur (Bailey, 1955 ; Turner and Fraser, 1956 ; Black and Harken, 1957), and valvotomy may be incomplete (Bailey, 1955 ; Turner and Fraser, 1956 ; Windsor, 1956). Wood (1954) concluded that heavy calcification is a serious drawback to surgery, not only because it suggests an appreciable degree of associated incompetence, but because it is also likely to favour the production of incompetence at operation. Black and Harken (1957) take a more optimistic view, stating that some of their best results were in patients with valvular calcification.

Calcification of the mitral-valve leaflets is a consequence of a previous rheumatic infection, is commoner after middle age, and occurs more often in males than females (Epstein, 1940 ; Turner and Fraser, 1956). Extension of calcium to the annulus in rheumatic cases is relatively uncommon and usually occurs after the age of 40 (Epstein, 1940). The mitral annulus alone can be involved in the absence of a previous rheumatic infection. It may be found in otherwise normal hearts after middle age, and in contrast to rheumatic calcification is slightly commoner in women. Simon and Liu (1954) found annular calcification in 10% of unselected hearts examined at necropsy. Such calcification is functionally not significant ; its importance is that it may be misinterpreted radiographically as being due to infiltration of the valve leaflets.

Calcium on the mitral-valve leaflets in a case of mitral stenosis is often suspected at the bedside, the associated valve rigidity modifying the characteristic auscultatory signs. The loud first sound tends to become normal or muffled, the opening snap disappears (Vaquez, 1894 ; Wolferth and Margolies, 1937 ; Wynn, 1953), and a systolic murmur is often present (Wynn, 1953).

The raised left atrial pressure in mitral stenosis causes the valve orifice to remain open until the onset of ventricular systole, when its sudden closure is audible as an accentuated first sound. With calcification and rigidity of the valve orifice, the edges are unable to snap together, so the first sound is characteristically normal or muffled. However, the first sound may be accentuated despite calcification (Wynn, 1953 ; Davies and Bucky, 1959). In Wynn's series of 60 patients with heavy mitral-valve calcification, the first sound was accentuated in 55%. In many patients with valve calcium a muffled first sound may become accentuated with tachycardia (Wynn, 1953).

The opening snap of the mitral valve occurs at the end of the period of isometric relaxation of the left ventricle, when the atrio-ventricular gradient is reversed. It may be due to sudden billowing of the aortic cusp into the left ventricular cavity (Sansom, 1881, 1892 ; Vaquez, 1894 ; Margolies and Wolferth, 1932), or to movement of the stenotic valve diaphragm deep into the left ventricle (Leatham, 1958). The latter is possibly the correct explanation, because rigidity and calcification of the valves does not always result in loss of the opening snap. Wynn found it to be present in 48%. The opening snap is absent in pure mitral incompetence (Brigden and Leatham, 1953).

The first sound may also be damped by associated mitral incompetence or a high pulmonary vascular resistance (Wood, 1954 ; Goodwin *et al.*, 1955). In addition to the above two factors, the opening snap may disappear in the presence of associated aortic incompetence, perhaps because the reflux into the left ventricle interferes with the sudden billowing of the aortic cusp of the mitral valve (Wood, 1954).

Calcium deposition on or around the valve orifice may also prevent effective closure during ventricular systole, hence some incompetence is often present despite otherwise severe stenosis. Wynn (1953) observed a systolic murmur in 80% of patients with heavy calcification. Goodwin *et al.* (1955) found that 10 of their 28 patients with mitral-valve calcification submitted to valvotomy had some incompetence. However, calcification is uncommon with pure incompetence (Goodwin *et al.*, 1955 ; Wood, 1956 ; Linko and Sysimetsä, 1958).

Radiology

Valvular calcification, if extreme, may be recorded on a teleradiogram. It is seen comparatively commonly in cases of calcification of the aortic valve, but rarely in the mitral. Klason (1921) was one of the first radiologists to report seeing mitral-valve calcium at fluoroscopy, after which fluoroscopy has remained the standard method of demonstrating intracardiac calcification. However, since Hohenner (1940) published a

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tomogram showing a partially calcified mitral ring, the use of body-section radiography has become increasingly more common. Davies and Steiner (1949) used tomography to demonstrate aortic-valve calcium, and Soloff *et al.* (1954, 1955) have emphasized its superiority in the demonstration of mitral calcium. Apart from making a permanent record of the calcium and allowing the clinician a more accurate and more leisurely assessment of its extent, tomography is more likely to show slight to moderate degrees of calcification than is radioscopy (Soloff *et al.*, 1955; Davies and Bucky, 1959).

Present Investigation

The object of this study was to examine the efficacy of mitral valvotomy in a series of patients with mitral-valve calcification.

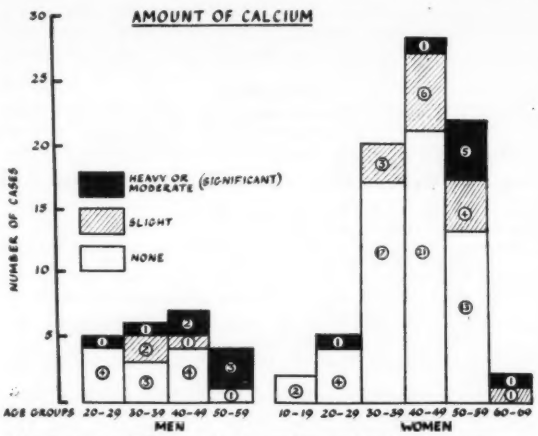
Material.—A total of 109 patients were submitted to valvotomy from October, 1954, to October, 1958. Eight were excluded from the study either because aortic or tricuspid valvotomy was performed simultaneously with the mitral or because of severe aortic incompetence. The 101 patients finally analysed comprised 22 men and 79 women, and all had dominant mitral stenosis pre-operatively: if other valves were affected, their effect on cardiac function was judged to be minimal. Valvotomy was carried out by Mr. W. P. Cleland, Mr. L. L. Bromley, Mr. H. H. Bentall, or their associates.

Methods.—At operation the calcium on the mitral-valve leaflets was graded as slight (+) when only small particles were palpable, moderate (++) if one leaflet or commissure was moderately infiltrated, and heavy (+++) if one leaflet or commissure was heavily calcified, or if both leaflets or commissures were either moderately or heavily calcified. In the discussion, moderate and heavy calcification are referred to collectively as "significant." A jet of incompetence, when present, was graded as minimal (+) when it could just be felt, moderate (++) if more definite, and severe (+++) if it reached the atrial wall and produced a systolic thrill. The valvotomy was considered to be "good" if the final orifice diameter was greater than 3 cm., "fair" if it was 2.5–3 cm., and "poor" if less than 2.5 cm. Subjective improvement post-operatively was noted as "good" if there was marked improvement in effort tolerance with ability to do housework or to work full time, "fair" when effort tolerance was definitely improved but the patient required help with housework or was restricted to part-time work, and "poor" if effort tolerance remained unchanged.

Results

Mitral-valve calcium was found in 32 patients, and in 15 it was moderate or heavy. It was most common in the fifth decade, and occurred more often in men (see Chart). Of the 10 men with calcium, it was moderate or heavy in seven, whereas in the 22 women it was significant in only eight. Tomograms were performed in 14 of the 15 patients with moderate or heavy calcium, and it was visible in each case. In the 17 patients with slight calcification calcium was visible in three.

No evidence of incompetence was found at operation in 81 patients, and 28 of these developed a jet of incompetence after valvotomy, in each case an apical pansystolic murmur being audible subsequently. Mitral incompetence occurred more commonly in patients with



Mitral-valve calcification in 101 patients submitted to valvotomy.

significant calcification, but the difference is not great (Table I). Instrumental dilatation with a valvulotome, or more recently with a transventricular dilator, was carried out in 38 patients. A better split resulted from an instrumental than from a digital split (Table II), which was most striking in the case of calcified valves (Tables III and IV). However, mitral incompetence was more frequent after instrumental dilatation (Table V). A valvulotome was used in nine patients, and a transventricular dilator in 29. A good split was obtained in 26 of the 29 patients on whom the transventricular dilator was used, and in 21 the split was greater than 3.5 cm. The results were especially gratifying in five patients with significant calcifications, where the split was good in four, and greater than 3.5 cm. in two, whereas in 10 patients with significant calcification whose valves were dilated digitally the split was good in only four, and in none was it greater than 3.5 cm. Four of the five poor valvotomies obtained instrumentally followed the use of the valvulotome.

TABLE I.—*Mitral Incompetence Produced at Valvotomy in Patients With and Without Valve Calcium*

Patients Without Pre-operative Mitral Incompetence	No.	No. in Whom Incompetence was Produced
Valve calcium absent	57	19 (33%)
Calcium present { Slight	17 } 24	6 (35%) } 9 (37%)
Calcium present { Significant	7 }	3 (43%) }
Total	81	28 (35%)

TABLE II.—*Size of Split Obtained With Digital and Instrumental Dilatation*

Method of Splitting Valve	No. of Patients	Split Obtained			Split > 3·5 cm.
		Good	Fair	Poor	
Digital	63	42	13	8	19 (30%)
Instrumental	38	29	4	5	22 (58%)
Total ..	101	71	17	13	41

TABLE III.—*Size of Split with Digital and Instrumental Dilatation in 15 Patients with Significant Mitral-valve Calcification*

Method of Splitting Valve	No. of Patients	Split Obtained			Split > 3·5 cm.
		Good	Fair	Poor	
Digital	10	4	4	2	—
Instrumental	5	4	1	—	2
Total ..	15	8	5	2	2

TABLE IV.—*Seven Patients with Significant Mitral-valve Calcification and No Pre-operative Mitral Incompetence*

Case	Age and Sex	Pansystolic Murmur Pre-operatively	Valve Calcium	Degree of M.I. Produced at Operation	Size of Split	Method of Splitting Valve	Pansystolic Murmur Post-operatively
A	53 M	0	+++	0	Poor	Digital	0
B	41 M	0	+++	0	Fair	,,	0
C	54 M	0	+++	0	,,	,,	0
D	54 F	0	++	0	Good	Instrumental	0
E	61 F	0	+++	+	Fair	Digital	Grade 1
F	53 F	0	+++	+	Good	Instrumental	,, 1
G	56 F	0	+++	+	,,	,,	,, 3

TABLE V.—*Incompetence Produced with Digital and Instrumental Dilatation in 81 Patients with No Initial Mitral Incompetence*

Method of Splitting Valve	No. of Patients	Incompetence Produced		
		+	++	+++
Digital	49	9	2	1
Instrumental ..	32	12	2	2

Associated mitral incompetence was diagnosed pre-operatively in 21 patients on the basis of an apical pansystolic murmur, and in 20 of these a systolic jet of valvular incompetence was felt at operation. Six of the patients were men and 14 were women. Five of the six men had significant calcium, whereas it was found in only 3 of the 14 women. One patient died 48 hours post-operatively after an aortic bifurcation embolus. Details of the remaining 19 are found in Table VI. The degree of incompetence was increased in 10 (Cases 1–10), and it remained unchanged in nine (Cases 11–19). Valvular calcification did not seem to increase the risk of making incompetence worse. Very few patients from this group have been followed for a sufficient period to enable any definite conclusions to be drawn regarding long-term results. However, the results so far are generally poor (Table VI) and do not appear to correlate with the presence or absence of calcium or the adequacy of the valvotomy, the important factor being the presence of significant mitral incompetence pre-operatively.

Ninety-five patients had critical mitral stenosis—that is, a valve diameter of 1.5 cm. or less—and in 31 the diameter was less than 1 cm. Three of the six patients with valve diameters greater than 1.5 cm. had associated mitral incompetence.

Emboli occurred at operation in two patients with valvular calcium. Calcification in each case was slight; both patients died after embolectomy, and there was no operative or necropsy evidence of calcific emboli.

The classical auscultatory signs of mitral stenosis were found to be modified in about half of the 15 patients with significant valvular calcification. Out of seven with pure stenosis the first sound was accentuated in four and normal or diminished in three. The opening snap was absent in one patient only. In the eight patients with associated incompetence the first sound was accentuated in four, normal or diminished in three, and the opening snap was absent in three.

Discussion

Instrumental dilatation of the mitral valve was used in patients on whom valvotomy could not be obtained digitally. An adequate valvotomy was possible in practically every case, especially with the use of the transventricular dilator, even in patients with calcified valves. However, it does appear that instrumental dilatation may give rise to mitral incompetence more often than does digital dilatation.

The functional effects of minimal incompetence after mitral-valve surgery have not been adequately studied, nor has there been a long-term study of any large series of such patients. Bailey *et al.* (1954) and Belcher (1956) are of the opinion that it is of little or no consequence, and this view is commonly held. An adequately dilated yet slightly incompetent valve would seem to be preferable to one which is competent yet insufficiently split. A detailed appraisal of transventricular valvotomy is planned (Cleland *et al.*, 1960), for the value of this method is regarded as not yet finally proved.

There is some evidence that restenosis of the mitral valve is less likely to occur when both commissures are completely divided than when commissurotomy is incomplete (Wilcken, 1960).

The tendency to produce mitral incompetence does not appear to be greatly increased in the presence of calcium. If incompetence is present pre-operatively, the results of valvotomy are not good. The presence or absence of calcium, the size of the split obtained,

TABLE VI.—*Nineteen Patients Who Came to Mitral Valvotomy With Associated Mitral Incompetence*

Case	Age and Sex	Pansystolic Murmur Pre-operatively	Valve Calcium	M.I. Before Split	M.I. After Split	Size of Split	Method of Splitting Valve	Pansystolic Murmur Post-operatively	Result and Period of Follow-up
1	27 M	Grade 1	+++	++	+++	Fair	Digital	Grade 2	Good—3½ years
2	55 F	,, 2	++	+	++	Good	,,	,, 4	Died of congestive cardiac failure after 1 year
3	63 F	,, 2	+	+	++	,,	Instrumental	,, 4	Poor—3 months
4	47 F	,, 2	0	+	++	,,	,,	,, 4	Fair—6 ,,
5	50 F	,, 2	0	+	++	,,	Digital	,, 4	No follow-up
6	43 F	,, 1	0	+	++	,,	,,	,, 2	Poor—6 months
7	32 F	,, 3	0	+	++	Fair	,,	,, 3	,, —7 ,,
8	41 F	,, 2	0	+	++	,,	,,	,, 4	,, —4 years
9	44 F	,, 2	0	++	+++	Good	Instrumental	,, 4	,, —2 ,,
10	41 M	,, 1	+++	+	+	,,	,,	,, 3	Good—6 months
11	32 M	,, 3	+++	++	++	,,	Digital	,, 3	,, —2 years
12	42 M	,, 3	+++	+++	+++	Poor	,,	,, 3	Died of congestive cardiac failure after 3 years
13	52 M	,, 1	+++	++	++	,,	Instrumental	,, 1	Fair—3 months (has severe emphysema and cor pulmonale)
14	52 F	,, 1	+++	+	+	Fair	Digital	,, 1	Poor—1 year
15	21 F	,, 3	+++	++	++	Good	,,	,, 3	Fair—1 ,,
16	42 F	,, 2	0	+	+	,,	,,	,, 2	Good—1 ,,
17	52 F	,, 3	0	++	++	,,	,,	,, 3	Died of congestive cardiac failure after 6 months
18	30 F	,, 2	0	+	+	,,	,,	,, 2	Good—1 year
19	23 M	,, 2	0	+	+	,,	Instrumental	,, 2	,, —1 ,,

and the worsening of incompetence already present do not seem to have any influence on the final result. The poor results of valvotomy in this group of patients are probably due to destruction of the greater part of the valve by rheumatic disease, the mechanism of which cannot be restored by simple division of the commissures. However, in some cases with calcium deposition the leaflets are relatively supple and non-shrunken, the calcium being found mainly along the free edge and on the adherent commissures. Such leaflets are capable of function if they can be freed. Incompetence in these patients is due mainly to calcium along the valve orifice preventing effective closure during ventricular systole, rather than to destruction of the leaflets. This is the probable explanation of some of the good results which may be obtained in patients with heavy valve calcification and associated incompetence.

If valvotomy is indicated in a patient with pure mitral stenosis the presence of valvular calcium should not unduly influence the decision for surgery, but if there is associated mitral incompetence then a poor result is likely.

The danger from calcific emboli during valvotomy does not seem to be very great. Bailey (1955) is of the opinion that emboli are more likely to occur from valves where calcification is slight. In such valves small fine particles of calcium project on the valve edges which may be readily dislodged at operation. Such particles are likely to occur on mobile valves, so they are not suspected clinically, nor are they visible radiologically. The possibility of calcific emboli occurring in any given case is insufficient reason for withholding surgery.

Fourteen of the 15 patients with moderate or heavy calcification had tomograms done, and calcium was demonstrated in each case, confirming that significant valvular calcification is practically always visible by tomography. Calcification was also demonstrated by tomography in three other patients in whom valvular calcium at operation was found to be slight. The patients were a man of 47 and two women of 44 and 58 years, and it is considered that the calcium in these patients was in the annulus. In older patients annular calcium may be readily confused with valvular calcium. Conventional radiography and tomography are of little help in distinguishing its site. Study of the valve movements under the image intensifier may resolve this difficulty. It was not found possible to grade the degree of calcification seen on the tomogram in this series.

The occurrence of calcification more commonly after middle age, and more often in males in this study (Chart), is similar to the experience of other authors (Epstein, 1940; Turner and Fraser, 1956). Also, when calcium is found it is more likely to be moderate or heavy in men than in women.

Eight of the 15 patients with significant calcification had associated mitral incompetence—an incidence of 54%, which is the approximate incidence found in other surgical series (Wood, 1954; Mounsey and Brigden, 1954; Goodwin *et al.*, 1955; Turner and Fraser, 1956). Of the six men with mitral incompetence, five had moderate or heavy valve calcium, whereas, of the 14 women with incompetence, calcium was significant in only three. Men with dominant mitral stenosis and associated mitral incompetence appear to be much more likely to have significant calcium on the mitral valve than are women similarly affected. Valvular calcification is uncommon with pure mitral incompetence (Goodwin *et al.*, 1955; Wood, 1956; Linko and Sysimetsä, 1958).

The presence of an opening snap in 11 of the 15 patients with significant calcification differs from the findings of Wynn (1953) and Davies and Bucky (1959), who found it in a considerably smaller proportion of their cases.

An apical pansystolic murmur was found to be the most reliable and consistent sign of associated incompetence in the presence of otherwise tight mitral stenosis. Incidental mitral incompetence was diagnosed prior to valvotomy in 21 patients on the basis of an apical pansystolic murmur radiating to the axilla and tending to diminish on inspiration. A jet of incompetence was felt at surgery in 20 of these patients, and no jet was felt in any patient without a pansystolic murmur. This finding is similar to that of Mounsey and Brigden (1954).

Summary

The incidence, pathology, functional effects, and surgical hazards of mitral-valve calcification are reviewed. In a series of 101 patients submitted to mitral valvotomy, 32 had valvular calcification, which was moderate or heavy in 15. About half the patients with significant calcium had associated mitral incompetence. Men with dominant mitral stenosis and associated incompetence are much more likely to have valve calcification than are women similarly affected.

Transventricular dilatation of the mitral valve has resulted in a good valvotomy in most of the patients where this method was used.

The incidence of post-operative mitral incompetence does not appear to be significantly greater in patients whose valves are calcified, compared with the non-calcified group. If incompetence is present pre-operatively the risk of worsening the incompetence is no greater in patients with valvular calcium. However, the results of surgery are generally poor in combined mitral stenosis and incompetence, and do not correlate with the presence or absence of calcium or the size of the valvotomy.

Tomography revealed calcium in every patient in whom it was moderate or heavy. The possibility of confusing annular calcification with valvular calcium is discussed.

In patients with significant calcification the first heart sound was normal or diminished in intensity in about half, and the opening snap was absent in about a quarter.

An apical pansystolic murmur was found to be the most reliable and consistent sign of associated mitral incompetence in the presence of otherwise tight stenosis.

The study was suggested by Dr. J. F. Goodwin, to whom I am indebted for his encouragement and advice. I am grateful to Mr. W. P. Cleland for allowing me to use his surgical records, and for his helpful suggestions. Thanks are also due to Dr. Aubrey Leatham and Dr. Arthur Hollman for offering valuable criticism, to Mr. L. L. Bromley for much useful discussion, and to Mrs. Angela Birbeck, who drew the illustration.

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INCIDENCE OF MITRAL VALVULAR DISEASE IN THE ELDERLY

BY

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Rheumatic heart disease is usually regarded as a condition which occurs mainly in young subjects. There have, however, been several reports of the occurrence of mitral stenosis in elderly patients after rheumatic disease many years previously (White and Bland, 1941; Cookson, 1949; Appel and Kossmann, 1951; Hebbert and Rankin, 1954; Johnson, 1959).

In these reports possible factors prolonging life in such patients have been discussed, and it has been stressed that women may rear large families despite this disability. Nevertheless, from none of these studies is it possible to obtain an estimate of the relative frequency of mitral-valve disease in persons over the age of 50 or 60. During the last few months we have been impressed by the number of elderly patients admitted to this hospital and found to have rheumatic heart disease with involvement of the mitral valve. We therefore decided to study the incidence of such disease of the mitral valve in different age-groups in this hospital, in an attempt to determine its relative frequency in persons in the later years of life.

Methods

The incidence of rheumatic disease of the mitral valve in patients dying in this hospital has been investigated by examination of consecutive post-mortem reports. We studied the records of 1,000 patients over 59 years of age, 500 patients aged between 40 and 59 years, and 250 patients between 20 and 39 years of age who died in the years 1947–58. In each of these groups we discovered between 22 and 32 patients with disease of the mitral valve which the pathologist, Dr. J. L. Edwards, considered to be of rheumatic origin. In all cases the valve cusps were thickened and deformed, with shortening of the chordae tendineae. In almost all specimens there was obvious stenosis of the valve and many were calcified.

Sheffield Royal Hospital is a general hospital for acute cases in which, over the past 11 years, necropsies have been carried out on 66% of the patients who died. There are approximately equal numbers of medical and surgical beds but no accommodation for the chronic sick or for patients with gynaecological or obstetrical complaints. Cardiac surgery is not carried out, and hence we believe that there is no special tendency for patients with mitral stenosis to be referred here. We have compared our findings with the figures given by the Registrar-General (1958) for deaths due to rheumatic disease of the mitral valve in England and Wales in 1957.

Results

Twenty-two cases of rheumatic disease of the mitral valve were found in 1,000 consecutive post-mortem studies of patients aged 60 or more. The incidence of disease of the mitral valve in patients aged 40 to 59 years was 6.4% and in patients aged 20 to 39 years it was 12.4% (Table I). In the older age-group the condition was found four times more frequently in females than in males, whereas in the younger patients mitral disease was approximately twice as common in females. In each age-group, and in both sexes, the incidence of mitral-valve disease found in this hospital was two or three times as great as that reported by the Registrar-General.

In our series the proportion of male patients dying from all causes was somewhat greater than that occurring in the Registrar-General's report and the proportion of younger patients was higher in our series (Table II).

Of the 22 patients aged 60 years or more who had mitral-valve disease, 15 were aged 60–69, six were 70–79, and one was 81. In 16 of the 22 patients the cardiac condition was diagnosed in life. However, the cardiac lesion seemed to be the primary cause of death in only

TABLE I.—*Incidence of Rheumatic Mitral Valve Disease Found at Post-mortem Examination of Patients Dying in the Sheffield Royal Hospital*

Age of Patient (Years)	Period of Survey	All Cases			Male			Female		
		Total	Mitral Disease		Total	Mitral Disease		Total	Mitral Disease	
			No.	%		No.	%		No.	%
60+	1958–1953	1,000	22	2·2 (0·7)	630	6	1·0 (0·5)	370	16	4·3 (1·0)
40–59	1958–1953	500	32	6·4 (2·8)	320	17	5·3 (1·6)	180	15	8·3 (4·8)
20–39	1958–1947	250	31	12·4 (4·6)	158	13	8·2 (2·9)	92	18	19·6 (7·7)

Figures in parentheses refer to the percentages reported by the Registrar-General for 1957.

TABLE II.—*Characteristics of the Population in Which the Patients With Mitral-valve Diseases Were Found (Registrar-General's Figures in Parentheses)*

Age in Years	Ratio Males/ Females All Patients	Percentage of all Patients in Each Age-Group	
		Males	Females
All ages	1·7 (1·1)		
60+	1·6 (1·0)	66·7 (76·6)	69·5 (84·5)
40–59	1·8 (1·6)	28·8 (20·1)	25·7 (13·1)
20–39	1·6 (1·4)	4·5 (3·3)	4·8 (2·4)

12 of the 22 patients. Of these 12, four died of congestive heart failure, two of pulmonary oedema, four after cerebral, aortic, or pulmonary emboli, and two after thrombosis of the pulmonary artery. Of the 10 patients in whom death did not appear to be directly attributable to the cardiac disease, six died shortly after surgical operations, one had a haematemesis from a gastric ulcer, one a myocardial infarct, one Hodgkin's disease, and one a cerebral thrombosis.

Sixteen of these elderly patients were female. Records were not complete in every case, but at least seven of them had borne children, one patient having had five offspring. Of the 15 patients about whom information was available, only two had had symptoms attributable to their mitral disease before the age of 50. Six of these 22 patients were known never to have been oedematous, but only two were in sinus rhythm a few weeks before death.

Discussion

We were surprised to find an incidence of rheumatic mitral-valve disease of 2.2% in patients dying in this hospital at 60 years of age or more. This confirms the impression of other authors that the condition is not so rare in the elderly as has been supposed. The discrepancy between our figures and those of the Registrar-General may be attributed to several factors. A relatively small proportion of old people die in a general hospital for acute cases, which is more likely to admit patients with congestive cardiac failure than with more chronic conditions. This produces an artificial elevation of the incidence of patients dying of mitral-valve disease in hospital. On the other hand, in a quarter of our elderly patients the diagnosis was not made before death; all but one of these patients were admitted to a surgical ward. It seems likely that the proportion of undiagnosed cases of mitral-valve disease is even higher in patients dying at home. Death in the elderly patient with mitral disease is often due to unrelated conditions, and mitral-valve disease would therefore not be the certified cause of death. For these reasons we believe that the incidence of rheumatic disease of the mitral valve in the elderly is much higher than that reported by the Registrar-General.

However, the Registrar-General's figures for the incidence of mitral-valve disease in younger patients are probably substantially correct, since such patients are less likely to die from intercurrent disease or to remain undiagnosed. The higher incidence which we found is probably due to the high proportion of these patients who died in hospital.

Summary

Of 1,000 consecutive necropsies on patients aged 60 years and over who died in the Sheffield Royal Hospital, 2.2% showed evidence of rheumatic disease of the mitral valve. The incidence in patients aged 40 to 59 was 6.4% and in patients aged 20 to 39 it was 12.4%.

The figures were shown to be higher than those of the Registrar-General for 1957. The possible reasons for this discrepancy are discussed.

We thank Dr. J. L. Edwards for allowing us to study his post-mortem reports and for helpful criticism. We also thank the physicians and surgeons of the Sheffield Royal Hospital for allowing us access to the records of their patients.

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IPRONIAZID IN TREATMENT OF ANGINA OF EFFORT

BY

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Iproniazid (" marsilid "), a derivative of isoniazid, was found to benefit patients with angina pectoris by Cesarman (1957), who claimed that complete relief from pain was produced in all of 41 patients studied. Subsequent reports have been conflicting, and the extent and nature of the side-effects have proved formidable. However, the early promise of the drug and the suggestion of a fundamentally different mode of action from the commonly used vasodilators were the reasons for this clinical trial, which was begun soon after the favourable report, and before the extent of the toxicity of the drug had become apparent.

The results are present of a controlled assessment of iproniazid in 51 patients with cardiac pain of effort.

Material and Methods

The methods employed were similar to those described previously (Fife *et al.*, 1957, 1958). Of the 51 patients included, 44 were men and 7 women. Their ages ranged from 37 to 65 years, averaging 54; 36 were in the age-group 45–60.

All patients gave a convincing history of angina of effort. Where dyspepsia was a feature, barium-meal examination (with particular search for hiatus hernia) and cholecystogram were performed. If any doubts on diagnosis remained, the patient was excluded from the trial. Evidence of myocardial infarction within the previous six months, and of anaemia or other debilitating disease, were also grounds for exclusion.

A 12-lead electrocardiogram was done in every case, and, if it was normal, six selected leads were taken after exercise to the point of inducing chest pain or tightness. Forty-one patients had electrocardiographic evidence of myocardial ischaemia while resting, and 10 of these had Q-wave evidence of previous myocardial infarction. Of the 10 patients with a normal electrocardiogram at rest, six had transient ST-T abnormalities after exercise. Particular attention was paid to the four with normal

electrocardiogram even after exercise; all of these had a clear response of their effort pain to glyceryl trinitrate.

Definite benefit from glyceryl trinitrate was claimed by 43 of the 51 patients; three were doubtful, and five had no benefit. The latter appeared to be using the drug in the correct manner, and their tablets were supplied from fresh stock.

No patient with a diastolic pressure above 120 mm. Hg was included. In 25 patients the diastolic pressure at the time of selection was over 95 mm. Hg, and in 26 it was less than that figure.

The severity of the angina was classified in arbitrary fashion as mild, moderate, or severe, according to the frequency of the attacks and the ease with which they were induced. Only two patients had frequent angina at rest.

The trial was conducted on a "double-blind" basis, using control tablets identical in appearance with iproniazid. The dosage was 50 mg. thrice daily after meals, and drug and placebo were each given for a three-weeks period in varying sequence. The first week was discounted, and the symptoms during the last two weeks were recorded as "much improved," "some improvement," or "unchanged or worse." Approximately half of the patients received the control tablet first. Most of the patients had previously participated in assessments of other drugs for angina.

Each patient was asked to complete a daily report card recording frequency of attacks of pain, side-effects of the tablets, etc.; and the number of pain-free days in each two-weeks recording period was noted.

Results

The results are shown in Tables I and II. Iproniazid appeared to benefit 31 patients, and the placebo 24 patients, a difference which is not statistically significant. When the patients were asked to compare the two tablets, 14 thought that iproniazid was better and 12 preferred the placebo; 12 thought that both were equally helpful, and 13 that both were useless. Again, this distribution of numbers is within that which might occur if both tablets were equally inert.

Towers and Wood (1958) found that the greatest benefit occurred in the severe cases, and Table I suggests that the present series might support this view. However, when the severe cases were compared with the remainder by statistical calculation it emerged that the apparent superiority of the drug over the placebo in the severe cases was just under the 5% level of statistical significance. The possibility is not excluded, however, that a larger series might have shown a significant benefit of the drug in severe cases.

Table II, which shows information about pain-free days derived from the patients' report cards, does not suggest any significant difference between iproniazid and the placebo in this respect.

Side-effects from the therapy were similar to those reported by previous workers, and were much commoner from iproniazid than from the placebo. Thirty-six patients attributed symptoms to iproniazid and seven to the placebo. The commonest of symptoms from iproniazid were dizziness, tiredness, weakness, and palpitation; but numbness of limbs, difficulty in micturition, impotence, constipation, dyspepsia, and other symptoms were also complained of occasionally. There was no correlation between improvement in the angina and the presence or absence of side-effects. Jaundice was not encountered.

TABLE I.—*Clinical Response to Iproniazid and Placebo*

	No. of Patients			
	Severity of Angina			Total
	Severe	Moderate	Mild	
Iproniazid helpful, placebo not	7 (3)	6 (2)	1	14 (5)
*Placebo helpful, iproniazid not	2	3	2	7
Both equally helpful	4	3	5	12
,, helpful, iproniazid better	0	0	0	0
*Both helpful, placebo better	0	5 (5)	0	5 (5)
Neither helpful	3	9	1	13
Total	16 (3)	26 (7)	9	51 (10)

Figures in parentheses are those described as "considerably improved." They are included in figures outside the parentheses.
* For statistical purposes these groups were combined ("placebo better") to give four groups; and mild and moderate cases were combined.

TABLE II.—*Relation Between Clinician's Assessment and Number of Pain-free Days While on Iproniazid and Placebo*

	Benefit from Iproniazid			Benefit from Placebo		
	Considerable	Some	Nil	Considerable	Some	Nil
No. of patients	5	26	20	5	19	27
Total pain-free days	54	167	41	68	156	27
Average (pain-free days per patient)	10·8	6·4	2·1	13·6	8·2	1·0

Discussion

Despite an extensive search over the years for a long-acting vasodilator capable of suppressing wholly or partly the pain of angina pectoris, none has been found to stand the test of time and remain by common agreement a remedy of proved efficacy. The report by Cesarman (1957) that iproniazid was effective in relieving anginal pain was thus especially interesting, as it appeared to act by some means other than coronary vasodilatation. The early favourable reports by Cesarman (1957) and Cossio (1957, 1958) were confirmed by Towers and Wood (1958), who, however, dispensed with a control series.

It had early been recognized that side-effects from iproniazid were common, but a serious toxic action on the liver in certain patients was reported (*New Engl. J. Med.*, 1958) and this has limited any potential clinical usefulness it might possess.

Further controlled trials of the drug in angina pectoris have failed to confirm its value, and Dewar *et al.* (1959) and Snow and Anderson (1959) found it no better than dummy tablets in their patients. Our own results are in line with this experience. When our 51 patients were considered as one group, iproniazid was no more effective than the placebo in relieving cardiac pain of effort.

Towers and Wood (1958) were particularly impressed by the value of iproniazid in severe and intractable angina, and Snow and Anderson (1959) felt unable to deny that benefit might occur from the drug in certain severe cases. In the present trial, comparison of the severe cases with the remainder in their response suggested a possible benefit of the drug in the severe cases. Indeed, such was our impression during the course of the trial. This apparently better action in the severe cases did not reach the 5% level of statistical significance.

however, but the series was too small to allow of its dismissal. Iproniazid may have a value in severe angina.

The use of a drug with a very high incidence of side-effects tends to destroy the double-blind design of the therapeutic trial, as the clinicians can hardly fail to recognize which is the active drug. In such circumstances conclusions must be particularly cautious, and cannot claim the total lack of possible bias as fully double-blind trials.

With this in mind we would limit our conclusions to stating that we have been unable to confirm any striking value of iproniazid in angina pectoris; that, except in severe cases, it was of no greater efficacy than the placebo; and that even in the severer cases any possible benefit was at best marginal, numbers of such cases being too small, however, to be statistically conclusive.

Side-effects were frequent and troublesome, and were mainly similar to those experienced by others. Toxic jaundice was not encountered.

Summary

A controlled clinical trial of iproniazid in 51 patients with angina of effort is reported.

With the possible exception of its use in severe cases, it was of no greater efficacy than the placebo.

Even in severe cases proof of its value was not conclusive.

Toxic effects were frequent and may sometimes be serious.

We thank Dr. S. D. Silvey, of the Department of Mathematics, Glasgow University, for advice and help with the statistical aspects; Dr. J. H. Wright for helpful criticism; and Messrs. Roche Products Limited for supplies of marsilid and placebo.

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Changing social attitudes towards mental health, the development of an awareness of the benefits that accrue from early treatment, and a growing public confidence in the service which is available are factors probably contributing to the increase in voluntary "boarders" entering mental hospitals in New Zealand. These comments are made in the annual report on mental health statistics which has just been released. The rate of voluntary boarders entering hospital has risen from 13.4 per 100,000 of population in 1938 to 46.7 in 1958—an increase of almost 300%. In the same period the increase in the admission rate for patients was 19.8%. A total of 3,741 people were admitted to mental hospitals in New Zealand in 1958. Of the persons "discharged out-right" from mental hospitals in 1958, 19.8% were in mental hospitals for less than one month, 49.9% were in hospital one month and under three months, and 20.3% were in between three months and six months.

ANTIBIOTIC SENSITIVITY TESTS

THE SPECIAL REQUIREMENTS IN OPHTHALMOLOGY

BY

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Little is known of the concentrations that are reached in the conjunctival sac from the application of drops and ointments, but it is established that the intraocular levels reached with penicillin, streptomycin, polymyxin, and neomycin after subconjunctival injection are considerably in excess of the blood levels reached from systemic administration. The usual sensitivity tests, being based on the blood concentrations reached by the different antibiotics on systemic administration, do not give full information for guidance in local treatment, for an organism may be insensitive to a relatively low concentration of an antibiotic and yet respond to a higher concentration. That this is the case with some organisms commonly met with in ocular infection is shown by the findings recorded in the accompanying Table.

It will be seen that in a series of 24 penicillin-resistant strains of *Staphylococcus aureus* found insensitive to disks containing 10 units of penicillin, no fewer than 14 were sensitive to tablets containing 50 units of penicillin, while 22 of the 24 responded to 250 units. (Increasing the concentration does not, of course, affect all organisms. Thus in 69 strains of different Gram-negative bacilli insensitive to 10 units of penicillin, only 4 (all *E. coli*) were found to be sensitive to tablets containing 50 units, and only one more organism, *Proteus vulgaris*, showed sensitivity to 250 units.) Similarly, of 23 strains of pneumococcus, an organism known for its resistance to neomycin, only 3 responded to the standard test of 30 μg. of neomycin, but the incidence of positive responses rose to 17 with 150 μg.; while all the 23 responded to 750 μg. Chloramphenicol,

Sensitivity of Some Micro-organisms in Relation to Different Concentrations of Some Antibiotics

	Staph. aureus (Penicillin-resistant)	Pneumo-coccus	*Ps. pyocyanea* (a)*	*Ps. pyocyanea* (b)*	*Pr. vulgaris* and Allied Organisms (a)*	*Pr. vulgaris* and Allied Organisms (b)*	*E. coli*
	No. of strains used						
	24	23	17	8	21	13	10
Antibiotic	*No. sensitive*						
Penicillin:							
10 units ..	0	23	0		0		0
50 ,, ..	14		0		0		4
250 ,, ..	22		0		1		4
Neomycin:							
30 μg. ..		3	17	8	21	13	10
150 ,, ..		17					
750 ,, ..		23					
Chloramphenicol:							
30 μg. ..		23	15		13	1	8
150 ,, ..						7	
500 ,, ..			17		18		10
750 ,, ..						9	
Polymyxin:							
10 μg. ..				0			
50 ,, ..				6			
100 ,, ..				8			

* (a)(b) Two different experiments with a different range of antibiotics.

which gave a high incidence of efficacy against Gram-negative bacilli, including *Pseudomonas pyocyanea,* also gave better results when the higher concentrations were used; of 61 different Gram-negative bacilli, 37 were sensitive to tests with 30 μg.; with tablets containing 150–750 μg., another 17 organisms proved sensitive, leaving 7 out of 61 unresponsive. The same trend is seen with polymyxin. While none of the eight strains of *Ps. pyocyanea* studied was sensitive to disks containing 10 μg., six responded to 50 μg., and all the eight responded to 100 μg.

These observations help to explain why occasionally a satisfactory result is obtained clinically by the use of massive doses of penicillin subconjunctivally when the organism is reported as penicillin-insensitive. Likewise, control by neomycin of experimental infection by pneumococci is explained by the fact that the dose used (0.5 g. subconjunctivally) gives high concentrations which would be effective against pneumococci which on the ordinary testing might well be reported as insensitive to neomycin.

At present the agents suitable for subconjunctival injection are penicillin, streptomycin, neomycin, and polymyxin (and there is promise in soframycin, of which, however, we have no experience). Streptomycin has distinct limitations in that it is not well tolerated locally and is productive of sensitization. Polymyxin has a limited range of action and is not free from local irritative effects. Penicillin and neomycin are the two agents that can be used readily as a subconjunctival injection, but neomycin is a toxic substance that has to be used with care. Chloramphenicol would be almost ideal for subconjunctival injection, if it were not so insoluble that it has to be used as a suspension of its micronized form, with a maximum possible injection of 0.75 ml. of 15% suspension containing in all some 100 mg. The tetracyclines are entirely unsuitable for subconjunctival use, as they are both insoluble and locally irritative. Information on the relative efficacy of the higher concentrations of these different agents, while it helps in making a choice in any particular case, therefore still leaves considerable problems.

It would seem desirable to establish the following simple routine in reports on the sensitivity of organisms in eye swabs—possibly in all cases, but certainly in infected eyes. One Petri dish should carry six disks or tablets containing the standard strengths for the commonly used antibiotics in ophthalmology: penicillin 10 units, streptomycin 20 μg., chloramphenicol 30 μg., tetracycline 30 μg., neomycin 30 μg., and polymyxin 10 μg. A second and third Petri dish would contain the same agents in 5 times and 25 times the concentration. The results so obtained can easily be set out in three columns, giving the clinician clear guidance on the relative efficacy of the different antibiotics in different concentrations for the organism under consideration. A simpler procedure would be to use one Petri dish for penicillin and neomycin, each agent in the three strengths suggested; a second Petri dish would complete tests on other antibiotics in one strength only.

We are indebted to Dr. F. S. Gorrill and Messrs. Evans Medical Supplies for their interest and generosity in supplying specially prepared sensitivity tablets for this study. Dr. S. T. Cowan, of the National Collection of Type Cultures, and Dr. R. I. N. Greaves, of the University Pathology Department at Cambridge, have helped with cultures. We are obliged to Dr. L. Hewlett, of the Royal Eye Hospital, and to Dr. J. Ungar, of Glaxo Laboratories, for advice.

INCIDENCE OF GLYCOSURIA AND DIABETES MELLITUS IN A GENERAL PRACTICE*

BY

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The importance of diagnosing diabetes mellitus early has been recognized for some years, yet many cases are not discovered until the onset of one of the complications of the disease. Joslin *et al.* (1946) stated that the only way to diagnose the disease in its early stages was by more frequent examination of the urine, not only of patients attending for consultation but also of persons who were supposedly healthy. The magnitude of the undiagnosed diabetic population will not be known until attempts have been made to find the true incidence of the disease. Diabetes is not notifiable, hence little information is available regarding its incidence. Tunbridge (1953) estimated that there were 150,000 diabetics in this country, and, because the proportion of the population over 40 years old was rapidly increasing, he estimated that within 20 years there would be half a million diabetics, or nearly 1% of the population. Andrews (1957), in a survey in West Cornwall, found an incidence of known cases of 5.6 per 1,000. In the United States also the disease is not notifiable, but several estimates have been made using data from death certificates which varied from 0.71% (Joslin *et al.*, 1946) to 0.48% (Marks, 1946).

Canvassing a population for cases of the disease gives only the prevalence of those that are known. An estimate of the true incidence depends entirely upon searching for cases as yet undiagnosed. Two surveys have been carried out which demonstrated that in the population there is a reservoir of undiagnosed diabetes (Blotner *et al.*, 1943; Blotner, 1946). In these surveys 45,000 and 69,000 men respectively had their urine tested for sugar, but, as these surveys were limited to men entering the Armed forces, no estimate could be made of the true incidence of diabetes in the population as a whole. The first systematic attempt to estimate the true incidence of the disease in a community was made by Wilkerson and Krall (1947) in Oxford, Massachusetts. Using postprandial blood and urine specimens, they tested 70.6% of the total population of 4,983. The incidence of the disease in the population tested was found to be 1.4%.

The second comprehensive diabetes-detection drive was carried out by Kenny *et al.* (1951) in Newmarket, Ontario. Using postprandial blood and urine specimens, they tested 81% of the population of 4,419 and found 54 cases of diabetes, 21 of them previously undiagnosed; the incidence of the disease was therefore 1.2%. In neither this survey nor in that of Wilkerson and Krall was there any attempt to classify the cases of non-diabetic glycosuria. Other diabetes-detection drives have been reported (Ford, 1949; MacBryde, 1949; Cauley, 1949; Sharkey *et al.*, 1950; Getting *et al.*, 1952; Fox, 1952; Loube and Alpert, 1954; Burn, 1956). Several of these were concerned with particular sections of the population, and in none was it possible to draw any definite conclusions on the true incidence of diabetes.

*From material presented as a thesis for the degree of M.D. in the University of St. Andrews.

The object of the present survey was to search for glycosuria in a general practice and to report the incidence of diabetes and non-diabetic glycosuria. An attempt was made to classify the causes of the latter.

Material and Methods

The practice is situated in Newcastle upon Tyne and is entirely urban. There are four doctors in partnership, and the total number of persons on the practice list at the time of the survey was 9,940. The first 1,000 patients tested were selected by making an alphabetical list of those whose surnames began with the first six letters of the alphabet. These patients were divided geographically and urine specimens were collected as described below. The remaining 991 patients were selected by taking every thirtieth card from the practice filing system and testing the urine of that person and all the members of his or her household. A total of 1,991 (20% of the total persons on the practice list) had specimens of urine tested for glucose. The reason for the change in the method of collection was that initially it had been the intention to test the whole practice, but this proved to be taking too long, and significant results could not be obtained without making allowance for the shifting population to and from the practice.

Urine specimens only were tested. Ideally, blood samples should have been examined also, but the practical difficulties of performing almost 2,000 blood-sugar estimations were too great. It was hoped that the disadvantages of urine-testing alone would be overcome by the method of urine analysis chosen for the survey.

Samples of urine were collected as follows. Specimen bottles were delivered personally to each household selected. Instructions were given to fill the bottle one hour postprandially next day. All specimens were then collected and tested. The possibility of patients testing their own urine specimens was considered, but this method was rejected on the evidence of Cauley (1949) and Getting *et al.* (1952), who reported the failure of diabetes-detection drives due to apathy of the public and its inability to carry out simple testing procedures.

For each person whose urine was examined a record card was filled in giving name, age, address, housing conditions, social group, general health, occurrence of obesity, and whether or not there was a family history of diabetes. For females a note was made of the obstetric history, with particular reference to birth difficulties and foetal gigantism.

In testing urine specimens "clinistix" was used as the screening procedure, and "clinitest" as a recheck if the result had proved positive with clinistix. The latter is a glucose-oxidase test, the limit of sensitivity being 0.1 g. of glucose per 100 ml. of urine (Hunt *et al.*, 1956). Clinitest is a modification of Benedict's qualitative test for sugar in urine. All those who gave a positive reaction to clinistix were offered a blood-sugar estimation. In most cases a glucose-tolerance test was performed, but in certain instances a single two-hour postprandial blood-sugar estimation was made instead. This applied to persons under 14 years and to adults who presented with symptoms of diabetes. The standard oral 100 g. glucose-tolerance test was performed with urine and blood samples taken with the patient fasting and at ½, 1, 1½, 2, and 2½ hours. Patients were instructed to eat a full diet during the week prior to the test except for the 12 hours immediately preceding. The test was performed in ambulant persons only. These tests were done in the pathological laboratory at the Newcastle General Hospital. The blood-sugar estimation used was the colorimetric method for true sugar first described by Haslewood and Strookman (1939) and modified by King (1946).

Diagnostic Criteria

Single Blood-sugar Estimations

Persons under 14 years of age who were found to have a two-hour postprandial blood-sugar level greater than 100 mg./100 ml. were referred for a glucose-tolerance test. If the reading was less than 100 mg./100 ml. they were assumed not to have diabetes and no further tests were performed. Persons over 14 years of age with symptoms suggestive of diabetes whose two-hour postprandial blood-sugar level was over 250 mg. were diagnosed as diabetic. Those with levels less than 250 mg. were referred for a glucose-tolerance test.

Glucose-tolerance Test

The interpretation of this test used in the survey was based on the criteria advocated by Harrison (1957).

Normal Curve.—Fasting level 80–120 mg./100 ml. of blood, peak level less than 180 mg. reached within 60 minutes, return to below 100 mg. within two hours, and no glucose in any urine specimen.

Diabetic Curve.—Fasting level greater than 120 mg. and glucose in one or more urine specimens: diabetes diagnosed. Peak level greater than 190 mg., time taken for return to below 100 mg. more than two hours even though fasting level normal, and glucose in one or more specimens of urine: diabetes diagnosed.

LAG-Storage Curve.—Fasting level normal, peak level greater than 180 mg., time taken for return to below 100 mg. two hours or less, and glucose present in one or more urine specimens.

Renal Glycosuria Curve.—Normal curve as described above, but glucose present in one or more urine specimens.

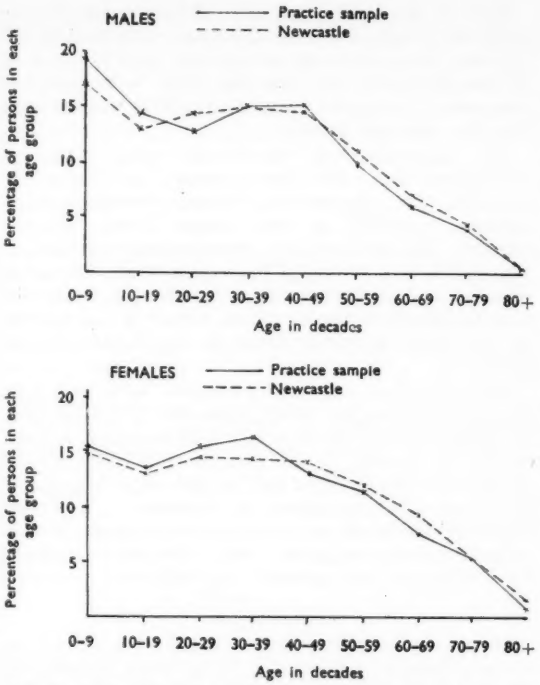
Hyperglycaemia without Glycosuria.—Fasting level 80–120 mg., peak level greater than 180 mg., and no glucose in any urine specimen.

Results of the Survey

During the survey, 1,991 persons (20% of the practice list) had a specimen of urine tested for glucose; 993 (49.9%) were males and 998 (50.1%) were females. A comparison of the age distribution of the practice sample tested and the age distribution of the population of the City of Newcastle (General Register Office, 1954) shows that the sample tested was fairly representative of the city as a whole (Table I).

TABLE I.—*Age Distribution of Population of Practice Tested in Relation to Age Distribution of Population of Newcastle. Age and Sex Distribution of Cases of Diabetes Encountered During the Survey*

Age in Years	Newcastle		Practice		No. of Diabetics in Each Group					
					New Cases		Known Cases		Total Cases	
	Total Persons	%	Total Tested	%	M	F	M	F	M	F
0–9	46,476	15·94	347	17·43						
10–19	38,214	13·11	284	14·26						
20–29	43,280	14·84	284	14·26						
30–39	43,197	14·81	323	16·22	1		1		2	
40–49	42,511	14·58	285	14·32		1				1
50–59	35,202	12·07	218	10·96	1	1	1	4	2	5
60–69	25,349	8·69	143	7·18		5		1		6
70–79	14,432	4·95	92	4·62		1		1		2
80–89	2,951	1·01	15	0·75			1		1	
Total	291,612	100·00	1,991		2	8	3	6	5	14



Age distribution of males and females in population of practice tested in relation to age distribution of population of Newcastle upon Tyne.

Taking the sexes separately, the similarity remains apparent (see Chart). The maximum difference in any one decade between the percentage of males in the practice sample tested and that of the city was 2.64% (0–9 years). For females the maximum difference was 2.33% (30–39 years).

An analysis of the social groupings of the population of the practice tested compared with the social groupings in the County of Northumberland (including Newcastle) shows that there was a higher percentage of persons in the practice sample in social groups IV and V than in the county and a smaller percentage in social group III (Table II).

TABLE II

Social Group	% Practice Sample in Each Group	% Population of County in Each Group
I	4·9	2·8
II	15·2	12·1
III	34·0	53·0
IV	26·1	19·7
V	19·8	12·4

Glycosuria.—Of the 1,991 persons tested 105 were found to have glycosuria—an incidence of 5.27%. Only 49 (46.7%) of these gave a positive result with clinitest. However, 62 of the 105 cases showed an abnormal blood-sugar reading on subsequent examination. Of the remaining 43 cases, 34 (32.4%) had a normal blood-sugar reading. These comprised 27 adults with normal tolerance tests and 7 children who had a single post-prandial blood examination only. Nine cases (8.6%) had no blood examination performed. Of the 105 glycosurias 58 (55.2%) were males and 47 (44.8%) were females. Glycosuria was uncommon in the age-groups 0–19 and 70-89. The highest incidence occurred in age-group 30–39.

Blood-sugar Estimations. — Seventy-five glucose tolerance tests and 11 single postprandial blood-sugar estimations were performed. Nineteen glycosurias did not have blood-sugar values estimated. Nine of these were known diabetics and one was a known case of lag-storage glycosuria. All these cases had been investigated previously at the diabetic clinic of the Newcastle General Hospital, and the results were available. Nine subjects had no blood examination—six refused the test, one was suffering from mental illness, one was senile, and one died from a dissecting aneurysm of the aorta before the test could be performed.

Diabetes.—Nineteen cases of diabetes were encountered during the survey—an incidence of 0.95%. Nine of these were known previously—an incidence of 0.45%. The remaining 10 were diagnosed as a result of the survey. Thus 52.6% of the total diabetics encountered were newly discovered. Fourteen of the nineteen cases were female and five were male. Thirteen were found in age-group 50–69 years (Table I). Six cases (31.6%) gave a family history of diabetes compared with only 6.34% of the total practice sample tested. Nine patients (47.4%) were either obese at the time of the survey or gave a history of having been so at some time. Four gave a history of obstetric difficulty—three of them with a history of foetal gigantism (birth weight over 10 lb.).

Previously Known Cases.—The ages of these patients ranged from 37 to 82 years, the mean age being 58.7 years. The highest incidence (five cases) occurred in age-group 50–59 years. The average duration of the disease was six years. Insulin treatment was being given in four cases ; the remainder were being treated by diet alone.

Newly Discovered Cases.—The ages of these cases ranged from 35 to 70 years, the mean age being 57.5 years. The highest incidence (five cases) was found in age-group 60–69 years. All cases gave a positive reaction to both clinistix and clinitest ; therefore no case would have escaped detection if clinitest alone had been used as the screening method. The diagnosis was made by glucose-tolerance test in eight cases and by a single postprandial blood-sugar estimation in two. Only one patient had complained of symptoms of diabetes prior to the survey ; seven had symptoms on inquiry and three had no symptoms even after leading questions. Only one case subsequently required treatment with insulin, the remainder being treated successfully with diet alone.

Lag-Storage Glycosuria.—The incidence of this condition in the population tested was 0.85%, a total of 17 patients (15 males and 2 females). They were fairly evenly distributed throughout the age-groups 20 to 79, the mean age being 49.0 years. All gave a positive reaction to clinistix, but 10 gave a negative result with clinitest, of whom six had a peak blood-sugar value greater than 200 mg./100 ml. in the glucose-tolerance curve. None had symptoms suggestive of diabetes, but seven were considered to be borderline cases biochemically. The doubtful cases fell into two categories: those with a fasting blood-sugar value of 110–120 mg./100 ml., a peak greater than 180 mg. but with a curve falling to below 100 mg. within two hours ; and those with a fasting blood-sugar of less than 110 mg./100 ml., but after a peak greater than 180 mg. the hyperglycaemia was prolonged, reaching about 100 mg. at two hours. Only one case gave a family history of diabetes.

Renal Glycosuria.—Twenty-five cases (15 males and 10 females) were diagnosed as cases of renal glycosuria, an incidence of 1.26%. The ages of these patients ranged from 15 to 70 years, with a mean of 38 years. All gave a positive reaction to clinistix, but only 14 were positive to clinitest. None had a family history of diabetes.

Transient Glycosuria.—Twenty-seven cases of glycosuria were subsequently found to have normal glucose-tolerance tests.

Hyperglycaemia Without Glycosuria.—One case was found to have hyperglycaemia according to the tolerance test, but no glucose was detected in any of the urine specimens except in the initial screening sample. After a peak of 194 mg./100 ml. the curve fell to less than 100 mg. at two hours.

Children with Glycosuria.—Only seven cases (4 males and 3 females) of glycosuria were found in persons tested under the age of 15 years. None had a two-hour postprandial blood-sugar value greater than 100 mg./100 ml., and, as all were symptom-free, none was subjected to a glucose-tolerance test.

Discussion

The sample of the population tested seemed to be fairly representative of Newcastle as a whole from the point of view of age and sex. The method of collection of the urine samples worked well but was rather laborious. However, the two great enemies of diabetes-detection drives—namely, apathy of the public and its inability to perform the simplest of testing procedures (Getting *et al.*, 1952)—were overcome by using this system. It was hoped that the possibility of human error had been reduced to a minimum.

Clinistix was found to be an excellent method for the mass detection of glycosuria. Only 49 out of the total of 105 cases of glycosuria gave a positive reaction to clinitest. Twenty-four of those which gave a negative reaction to clinitest had an abnormal glucose-tolerance curve subsequently. All the cases of diabetes found as a result of the survey gave a positive reaction to both tests, but the results indicate that the extreme sensitivity of the glucose-oxidase test was necessary to uncover many cases of glycosuria, including some that have been classified as borderline cases of diabetes. The reason for this may have been that many persons submitted fasting urine specimens and not postprandial as instructed.

Over half the diabetics encountered were discovered as a result of the survey, suggesting that a large number of undiagnosed diabetics are present in the population. A total incidence of 0.95% is a smaller figure than those found in the two previous comprehensive surveys. Wilkerson and Krall (1947) found an incidence of 1.4% using slightly different criteria in the diagnosis of the disease. It is possible that five cases diagnosed as lag-storage glycosuria in the present survey would have been diagnosed as diabetes by Wilkerson and Krall. Kenny *et al.* (1951) found an incidence of 1.2%, but again the criteria of diagnosis used were not the same.

The diagnosis of frank cases of diabetes presented no problems. The association of symptoms, glycosuria, and hyperglycaemia made up a classical picture. Others had the typical diabetic type of tolerance curve. The difficulties of diagnosis were confined to the borderline cases.

Most of the newly discovered diabetics were in the upper age-groups; indeed, half of them were aged 60–69. All were mild cases except one, a man, aged 35 who was of low intelligence and also was found to be suffering from severe pulmonary tuberculosis. This was the only case that required insulin.

The incidence of lag-storage glycosuria was surprisingly high; but, unfortunately, no figures are available for comparison, mainly because many workers, especially in the United States, do not recognize the condition as a separate entity. Indeed, it seems likely that several of these cases would have been classified as diabetics by some authorities. The relatively high incidence of the condition found in the present survey seemed to justify its use in the classification of glycosuria.

There are two problems associated with both lag-storage glycosuria and renal glycosuria: first, they must be differentiated from diabetes; and, secondly, it must be decided whether or not they are prediabetic states. Joslin *et al.* (1946) stated that in their experience renal glycosuria never progressed to diabetes. However, Wilkerson and Krall (1953) in a follow-up study of their earlier survey suggested that allegedly harmless glycosuria may often precede frank diabetes.

Conclusions

The survey has demonstrated that there is a reservoir of undiagnosed diabetes in the practice population. There may be as many as one undiagnosed case for every one already known. The results have confirmed the importance of routine testing of urine for glucose. It would seem desirable to test the urine of all patients attending the surgery for consultation, regardless of their complaints. The ages of the newly discovered diabetics indicate that routine testing is of greater importance in persons over 40 years old, and it is suggested that they should have their urine tested annually.

The survey has indicated the value of diabetes-detection drives. The presence of so many undiagnosed cases of diabetes in an ageing population warrants the institution of large-scale detection campaigns similar to those already being carried out in the United States. These could be organized by individual diabetic clinics, but would require the co-operation of public health authorities and general practitioners.

The importance of the large number of cases of non-diabetic glycosuria uncovered by the survey is difficult to assess at the present time. All these cases, and especially those labelled as borderline cases of diabetes, will require careful follow-up.

Lastly, the survey has demonstrated once again the desirability of having a standardized method of performance and generally accepted interpretation of the glucose-tolerance test.

Summary

A survey to find the incidence of glycosuria and diabetes mellitus in a general practice in Newcastle upon Tyne is reported. Some 1,991 persons (20.03% of the total practice) had their urine tested for glucose. 105 cases of glycosuria were found—an incidence of 0.95%. Nine cases had been previously known and 10 were discovered as a result of the survey. The latter were found mainly in the older age-groups and the disease was mild in severity in most cases.

Seventeen cases of lag-storage glycosuria were found—an incidence of 0.85%. Seven were adjudged to be

borderline cases of diabetes and will require careful follow-up. Of the other cases of non-diabetic glycosuria 25 were classified as renal glycosuria, 27 as transient glycosuria, seven were children and were unclassified, and nine did not have blood examinations performed. One case was found to have hyperglycaemia without glycosuria on a glucose-tolerance test. The significance of these cases is discussed, and it is concluded that all will require reassessment at a later date.

The inference drawn from the study is that the number of undiagnosed diabetics present in the population is large enough to warrant the routine testing of urine for glucose, especially in the older age-groups. It is suggested that large-scale diabetes-detection drives should be started in this country on the same lines as in the United States.

My thanks are due to Professor R. B. Hunter, Dean of the Faculty of Medicine in the University of St. Andrews, for permission to publish material presented as a thesis for the degree of M.D. in the University; to Dr. G. O. Richardson, senior consultant physician at Newcastle General Hospital, for his interest and encouragement, and to Dr. B. E. Tomlinson, consultant pathologist in the same hospital, for his assistance with the glucose-tolerance tests. I am grateful to Ames & Co. for providing me with the clinistix and clinitest tablets.

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The Ministry of Health booklet, *The Feeding of Children from One to Five Years*, which has sold over 3,000 copies a year since it was first issued in 1942, is now available in a revised edition (H.M.S.O., price 1s.). It has been designed mainly to help those in charge of groups of young children to plan and prepare balanced, attractive, and varied meals. For this purpose, recipes in it are based on ingredients for ten children. There is, however, much general advice on the feeding of the under-fives, and on their emotional as well as their nutritional needs in the building of good health and good habits.

DEVELOPMENT OF CHEST PAIN IN MUNCHAUSEN'S SYNDROME

BY

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Pain in the chest of cardiac distribution is one of the less common symptoms of patients with Munchausen's syndrome. When, however, it has occurred, electrocardiographic changes indicating myocardial ischaemia have sometimes been found (Davidson, 1953; J. C. Barker, 1959, personal communication). In the case of a patient with Munchausen's syndrome reported below, the diagnosis of an acute myocardial infarction was repeatedly made on the basis of recurrent attacks of cardiac pain and certain electrocardiographic changes, though, in fact, the electrocardiographic pattern was that of the sickle-shaped R–T plateau type (Bedford and Thomas, 1954), a physiological variant usually associated with perfectly good health.

Case History

The patient was born in 1918. At different times he claims to be employed either as a clerk or as a publican. Since 1953, using one of two names, he has attended at least 16 hospitals in England and Scotland. His usual story is that of severe gripping pain situated across the front of the chest on both sides and often radiating up to the neck and down the left arm. The pain develops about half to one hour beforehand while he is walking or lifting heavy weights, etc. Physical examination is usually negative apart from showing an emphysematous type of chest. At times, however, he has sweated profusely, and on one occasion there was a fall in blood pressure to 95/60 mm./Hg. Almost always electrocardiography is performed, after which a diagnosis of an acute myocardial infarction is often made and he is treated accordingly in hospital with bed rest, sedatives, and anticoagulants. Sometimes the electrocardiographic changes are not considered to be typical of acute coronary artery disease, but in view of the history of chest pain he is admitted to hospital for further observation. On one occasion, however, the casualty officer of a certain hospital did not accept his story of pain in the chest even though he was dyspnoeic; after a complete physical examination, which was negative, the patient was discharged from hospital without electrocardiography or any further ado.

When the patient is admitted he is at first extremely plausible (he often gives a graphic account of his wartime exploits in the R.A.F., claiming to have taken part in the Moehne Dam raids), but subsequently he becomes very objectionable, especially towards the nursing staff, and almost invariably takes his own discharge against medical advice within a period of several days to a few weeks. While residing in one hospital he had several bouts of chest pain associated with sweating and hypotension for which he received numerous injections of morphine until it was realized that he was becoming addicted to this drug. At the same hospital he cut his wrists with a razor-blade, but his wounds were superficial and it was considered that the gesture was a psychopathic one rather than a true suicidal attempt. During all his visits to hospital he has remained afebrile (except on two occasions), and the white-cell count and erythrocyte sedimentation rate have been normal.

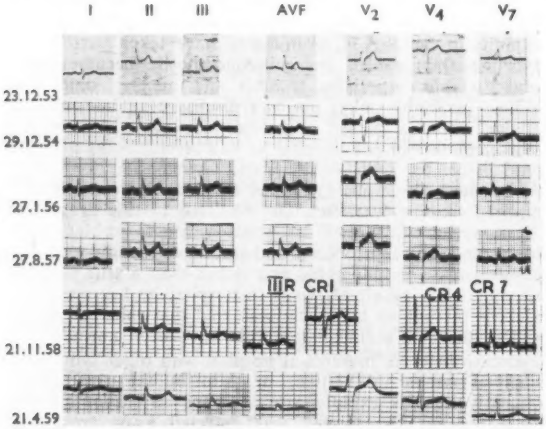
Occasionally he presents at hospital with other symptoms such as headache, vertigo, or pain in the right testis (recently he was explored for a supposed torsion of the testis but no abnormality was detected apart from the presence of a hydrocele). In February, 1959, he attended the out-patient department of Charing Cross Hospital with

a history of frontal headaches during the previous six months. At that time the blood-pressure was 120/85 mm. Hg, the heart sounds were normal, there were no signs of cardiac failure, and the retinal and other vessels appeared healthy. The urine was free of sugar and albumin. The other systems were also normal apart from an appendicectomy scar. The haemoglobin was 14.2 g./100 ml., the serum W.R. was negative, and the serum cholesterol was 200 mg./100 ml. The latter estimation had been performed two months previously at another hospital. It was decided to refer him to the psychiatric department, but he fled from the hospital before an appointment could be made.

Discussion

The sickle-shaped R–T plateau type of electrocardiographic pattern is perhaps not so well recognized as it should be outside cardiological centres. It consists of an elevated R–T segment with an upward concavity terminating in a high positive and sharply peaked T wave. The lowest point of the dipped R–T segment is closer to R than to the summit of T. In addition, the QRS complex is predominantly positive, there is frequently a well-marked Q wave, and the downstroke of R is notched, slurred, or may show an R^1. These changes are seen mainly in lead I or III as well as in the left chest leads. In contrast to acute cardiac infarction, reciprocal R–T displacement never occurs. Another point of distinction is that the RS-T segment which develops after an acute myocardial infarction is usually either straight or has an upward convexity—that is, cove-shaped. The sickle-shaped plateau curve must also be distinguished from the electrocardiographic changes which accompany pericarditis. In the latter condition, however, the RS-T segment may return to normal within a few days, and later on the T waves may become inverted. Moreover, the electrocardiographic changes associated with pericarditis are likely to be more widespread than in the case of the sickle pattern.

Bedford and Thomas stated that the sickle pattern is a non-specific one seen most commonly in subjects with good health. Occasionally, it is found in athletes and subjects with vagotonia or in patients with an effort syndrome liable to fainting attacks. Rarely it may be present in cases of coronary artery disease. The electrocardiograms of the patient under discussion (see Fig.) indicate that this sickle pattern is present in leads



Some examples of the electrocardiograms, showing the sickle-shaped R–T plateau pattern recorded in this patient between 1953 and 1959.

II and III and AVF as well as in some of the left chest leads. Furthermore, all the tracings are virtually identical, even though they were recorded over an interval of several years. If, in fact, the patient had sustained *repeated* episodes of acute coronary occlusion or pericarditis the pattern of the electrocardiogram would have undergone considerable alteration during this period.

Though it is considered that the electrocardiographic pattern of this patient is an example of the sickle-shaped R–T plateau curve as described by Bedford and Thomas, it must be stated that one cardiologist to whom these records were shown maintained that they displayed evidence of coronary arterial disease with signs of a limited infarction. This opinion was based on the presence of significant Q waves in leads II, III, and IIIR, the occurrence of low T waves in certain leads, depression of the T-U segment in CR4, and the appearance of a notch in CR7. This observer agreed that the sequence of events associated with the patient indicated that his symptoms were predominantly functional.

Apart from the electrocardiographic evidence, there are other reasons for viewing with suspicion the account given by this patient. Though the incidence of myocardial infarctions in young male adults may well be increasing, it must be unusual for a man in his late thirties to have such a rapid succession of acute coronary occlusions within a period of five years or so, especially in the absence of any predisposing cause such as diabetes mellitus or primary hypercholesterolaemia. Indeed, it is highly unlikely that any patient, irrespective of age or sex, would have survived under these circumstances. Another point is that though this patient occasionally displayed sweating and fever, and even, on one occasion, a fall in blood-pressure, there was never any other circumstantial evidence in favour of the diagnosis of an acute myocardial infarction such as signs of heart failure or an increase in either the white-cell count or erythrocyte sedimentation rate. As Todd (1959) has emphasized, all the available facts should be considered before the diagnosis of cardiac infarction is made in a patient complaining of pain in the chest. Finally, the curious mixture of speciousness and truculence culminating in self-discharge from hospital are forms of behaviour which have been seen not only in this patient but also in others afflicted with Munchausen's syndrome.

According to A. Small (1959, personal communication), patients with Munchausen's syndrome differ from malingerers and exhibitionists in that their attitude and symptoms are permanent rather than intermittent. Small further considers that Munchausen's syndrome is usually associated with organic disease, the treatment of which is often unsatisfactory. Occasionally the syndrome may be associated with developmental lesions such as opaque nerve fibres around the optic disk (Heathfield, 1957), or, as in this patient, a sickle-shaped R–T plateau electrocardiographic pattern. Any initial confusion in the diagnosis of such anomalies, provided it is obvious enough to the patient, may act as a trigger mechanism in certain susceptible individuals with an underlying psychopathic constitution and lead to the development of the syndrome. In this respect, Barker (personal communication) agrees that the condition is often iatrogenic, while Clyne (1955) has even suggested that the name Munchausen should be replaced by the term "misdiagnosis." In any event, a certain degree

of medical knowledge on the part of the patient would seem to be a prerequisite for development, even though Barker and Grygier (1958), among others, have encountered the condition in a subject with mental deficiency. In addition, it is likely that other factors such as illegitimacy (Grant, 1952) and drug addiction (Todd, 1951) play a part in some cases.

The reasons for the development of the syndrome in the case described here remain uncertain, though it is reasonable to suppose that the professional apprehension shown after the initial electrocardiogram was duly recognized by the patient and taken advantage of on subsequent occasions. Unfortunately, it has not been possible to discover whether electrocardiography was performed before December, 1953 (the first available record). It is conceivable, of course, that electrocardiography was originally carried out on account of genuine cardiac pain associated with a small coronary occlusion or acute pericarditis. Whether or not this was so, the possession of a sickle-shaped R–T electrocardiographic pattern has enabled the patient to simulate organic heart disease on numerous occasions during the past five years. It is certainly regrettable that the psychopathic origin of such behaviour is likely to prove a stumbling-block in his management and treatment in the future.

ADDENDUM.—After exercise the S–T segment of the sickle-shaped R–T plateau pattern returns to the isoelectric line. For this reason, if this patient attends other hospitals in the future it would be of interest to perform electrocardiography before and after exercise.

I thank those cardiologists who have kindly given their valuable advice regarding the interpretation of the electrocardiograms of this patient. I would also like to acknowledge the help given by the medical staff of the numerous hospitals which this patient has attended.

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Steady progress is being made in the campaign to rid Scotland of smoke, and clean-air exhibitions have recently been opened in Glasgow and Edinburgh. The Clean Air Council for Scotland—of which Sir DAVID ANDERSON is chairman—has been told that 26 town and county councils have already made smoke control orders or are considering making them. Altogether 90 local authorities have been urged to set up smoke-controlled areas. Arrangements are being made for appeals to householders in smog-prone areas to burn smokeless fuel or to use gas or electricity when conditions become bad. It is known that about half the smoke-polluting air comes from household fires. Some of this comes from the lighting of fires, and the council is having a new smokeless firelighter tested by its technical advisers. The possibility of an electrical firelighter for use in houses where there is no gas is also being studied. Another problem being examined is the effects of fumes from buses and other motor vehicles. The Clean Air Council for Scotland is in touch with the Clean Air Council for England and Wales in the whole field of smoke control.

INFANTILE SCURVY

BY

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That dietary deficiency of vitamin C remains a possibility is emphasized by instances of overt scurvy which, exceptionally, do still occur. The following examples in infants and children have been reported from England and Wales in the last decade.

Six out of 10 cases seen at the Hospital for Sick Children, Great Ormond Street, in 1947–9 were in mental defectives aged 23 months to 4½ years who were cared for at home by their parents. Their diet, perforce liquid or semi-solid, was mainly milk, custard, cereals, milk puddings, cakes, biscuits, and tea. Vegetables were refused, and orange juice was either refused or vomited and discontinued, or never offered (Beynon and Evans, 1951).

Derham (1950) describes the case of a 10-year-old girl who, in addition to a history of tuberculous peritonitis with prolonged diarrhoea, had perverse eating habits to which much attention had been paid, refusing fruit, green vegetables, milk, and potatoes.

Baber (1953) reports two cases. One patient at 9 months was still on cow's milk and cereal. Orange juice had caused vomiting and had been discontinued early. The other developed scurvy at 4 months while in hospital with gastro-enteritis, having had orange juice for two weeks only.

From a population of 250,000 in Cornwall, seven further cases were seen by Howells *et al.* (1954). These babies of 7 to 12 months had been fed on boiled cow's or National dried milk since birth ; none had had solids, and six had not had orange juice.

Reports of adult scurvy appearing in the same period (Riches, 1954 ; Dewhurst, 1954 ; Hughes and MacLennan, 1954) confirm Cutforth's (1958) finding that they fall predominantly into two groups: (1) old men living alone, failing to feed themselves properly ; and (2) those whose rigid diets, usually for peptic ulcer, exclude fruit and vegetables (save mashed potato) for periods of a year or more. One woman of 64 had had little but tea, sugar, beef extract, biscuits, bread, butter, and paste for 26 years (Glyn and Campbell, 1957).

Case Report

Scurvy in this child is reported because he was receiving a normal diet in an institution in which regular vitamin C supplements were given.

A boy of 15 months was admitted to hospital in 1958 with a painful swelling of one leg ; diagnosis ? osteomyelitis. Since he was 2 weeks old he had been in a pleasant home for deprived children run by nuns under medical supervision. Details of family and birth are unknown.

Previously normal, he had been listless for a fortnight with a swelling of his right thigh, and for five days he screamed on being handled. The sister, noting his gums to be swollen and to bleed, had in fact given him extra rose-hip syrup for two weeks. His appetite, usually good, had been poor for two days.

On examination he was fairly well covered, pale, and fretful, with a temperature of 101.8° F. (38.8° C.). He kept his right leg still in the classical "frog position"—that is, externally rotated and moderately flexed at hip and knee.

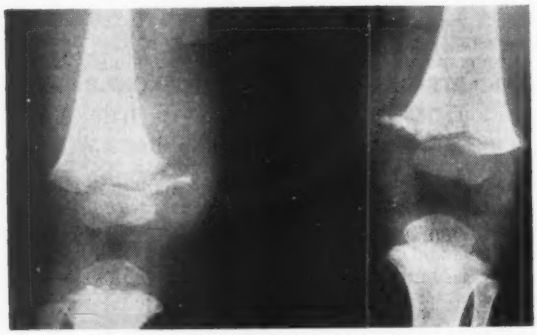

FIG. 1.—Radiograph showing characteristic changes in lower ends of femurs.

There was a diffuse, firm, warm swelling with crepitus above the knee, and the overlying skin, though shiny, was not reddened. He screamed when this was touched. Marked angular rib-beading at the costo-chondral junctions and a purplish-red swelling of the gums around erupted teeth were also noted. A positive Hess test demonstrated increased capillary fragility. There was no other physical abnormality.

Investigations.—A microcytic hypochromic anaemia: Hb. 56%; colour index 0.65. W.B.C. 9,000/c.mm. (polymorphs 50%, lymphocytes 44%). Urine—no excess of R.B.C.s. Serum calcium, phosphorus, alkaline phosphatase, platelet count, bleeding-time, and clotting-time were all normal. W.R. and Kahn test negative. The urine ascorbic acid content two and five days after starting treatment was 5 mg. and 3 mg./100 ml. respectively.

FIG. 2.—Radiograph showing marked calcification in subperiosteal haematoma at 18 days.

The radiographic changes seen in the lower ends of the femurs were characteristic (Fig. 1). These were: (1) an irregular line of relatively dense calcification at the epiphysial ends (the Trümmerfeld line) with the appearance of lateral spurs; (2) the Gerüstmark-zone of relative translucence on the metaphysial side of this; (3) the shadow of a large subperiosteal haematoma just starting to calcify; and (4) displacement of the right lower femoral epiphysis. Bone rarefaction and thinning of the cortex were not visible, possibly because extra rose-hip syrup had already been given.

He was given 500 mg. of ascorbic acid daily for three weeks, reducing to 200 mg. a day, coupled with oral iron and gallows traction to his legs.

After a week he was happier, was eating better, and his leg was less tender. He ran a temperature of 99–101° F. (37.2–38.3° C.) for 18 days, but no infection was found. By one month his gums were normal; haemoglobin 78%. At two months the rib-beading had disappeared. The Hess test remained positive until the sixth week. Radiographs showed marked calcification in the subperiosteal haematoma at 18 days (Fig. 2), and at seven weeks (Fig. 3) healing was advanced (left leg).

Discussion

The cause of this child's scurvy was not at first obvious. He had been given 50 mg. of ascorbic acid daily until he was 9 months old, and then, for six months, one teaspoon of rose-hip syrup a day. At 57 mg./fl. oz. (200 mg./100 ml.) this roughly equals 7 mg.

His diet for six months had been "farex," milk (about a pint (570 ml.), pasteurized and boiled), bread-and-butter, rusks, old potatoes (mashed), meat, cabbage *or* carrots, milk pudding, and plain cake. Banana, stewed apple, or orange juice was given no more than once a week. Uncooked, these vegetables could provide anything between 10 mg. and 130 mg. of ascorbic acid a day.

The minimum vitamin C intake which will prevent scurvy is not accurately known. 10 mg. daily is usually quoted, this amount having protected adult volunteers from scurvy for 424 days, and also cured six in whom the disease had been induced (Krebs, 1953). Lower figures have been suggested. Cruickshank (1959), for example, regards 7 mg. a day as protective for a baby, while Mottram and Graham (1956) suggest 4 mg.

This child developed scurvy while receiving something over 7 mg. a day for six months, having had an optimum dose previously, and there could therefore have been very little in his food.

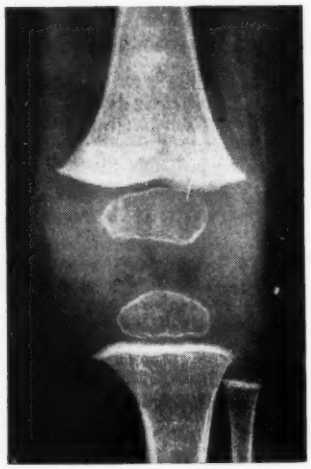

FIG. 3.—Radiograph taken at 7 weeks, showing advanced healing.

Losses could have occurred in several ways, and are perhaps particularly apt to occur in institutions. For example: (1) In storage. Vegetables, as opposed to fruit, rapidly lose their vitamin C at room temperature. (2) In cooking. Maximum losses occur if vegetables pass through the 65°–85° C. range, when plant oxidases are most active. The potatoes were in fact put in cold water and boiled, while the cabbage and carrots, dropped in large amounts into boiling water, almost certainly lowered the temperature below 85° C. (3) In keeping food hot, and in mashing potatoes. (4) In boiling milk *after* it has been pasteurized, which destroys most of the vitamin C. Boiling fresh milk for five minutes, however, does not (Woodruff, 1956).

The above case therefore emphasizes how a diet which is relatively fixed, as in an institution, and relies on every-day methods of preparing vegetables may be grossly deficient in vitamin C. Ebbs (1951) stated: "Gingivitis, a common finding in institutional groups of children and young people, if cleared by local treatment,

can be prevented from recurring by the administration of adequate amounts of vitamin C."

Clinically, the subperiosteal haematoma, the tenderness and "frog position" of his leg, plus marked radiological changes in rapidly growing bones were characteristic of infantile scurvy. Skin and subcutaneous haemorrhages, and hyperkeratotic hair follicles, seen in older patients, were absent. Anorexia, swollen gums, anaemia, and low-grade fever (probably due to blood-absorption) may be features of scurvy at any age.

Summary

Reference is made to 16 examples of scurvy in infants and children reported from England and Wales in the past 10 years. All but one failed to take a mixed diet containing fruit and vegetables due to (*a*) lateness in weaning (eight infants aged 7 to 12 months), (*b*) mental defectiveness (six children aged 23 months to 4½ years), or (*c*) food faddism (one girl of 10 years), and all were combined with failure to offer orange juice, or a substitute if refused or vomited. Malnutrition due to gastro-enteritis accounted for one at 4 months.

Of 17 adult cases reported over the same period, most were either old men living alone or people on restricted diets chiefly for peptic ulcers.

Scurvy occurring in a 15-months-old boy in an institution is described. The accepted minimum daily vitamin C requirement of 10 mg. had not been met by a mixed diet, including vegetables and a teaspoonful of rose-hip syrup containing about 7 mg. of ascorbic acid.

Reasons for the low dietary content are suggested, and the liability of this to occur in institutions is emphasized.

I am grateful to Dr. R. T. Jenkins, Dr. K. Mendl, and Mr. Mervyn Evans for their help and encouragement.

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"The increasing clarity of the atmosphere has been noted on many occasions during the year; the effects of the steady improvement in the condition of the atmosphere on health will take longer to become evident. Custom and a mistaken conception of comfort are difficult hurdles to overcome, but the response of the public to the measure for clearing the atmosphere has been very encouraging. Privy middens were once usual but are now unacceptable—in twenty years' time people will recount with amused censure and an air of superiority, 'Fancy! they had open coal fires.'" (*Annual Report on the Health of the City of Sheffield*, 1958.)

OBESITY IN CHILDHOOD

A CLINICAL TRIAL OF PHENMETRAZINE

BY

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Phenmetrazine ("preludin") is a synthetic derivative of ephedrine. It is not pharmacologically related to amphetamine. It has been much used in the treatment of obesity owing to its effect on the appetite. According to the manufacturers the primary action is on "the satiety centre in the hypothalamus. Satisfaction of appetite occurs sooner than normal. On the other hand, the urge to eat remains unaffected." The value of phenmetrazine in the control of obesity in adults has been demonstrated by several controlled investigations (Fazekas, Ehrmantraut, and Kleh, 1958; Leith and Beck, 1958; Patterson, 1959). There are also references in the literature to the value of phenmetrazine in the control of obesity in children (Bleckmann and Salus, 1955), but no clinical trial of the use of the drug in children has so far been published. For this reason the present study was undertaken.

Present Investigations

The obese children included in this investigation were treated as out-patients. They all weighed over the ninetieth percentile above the average weight for their age, and all were gaining weight at the beginning of the trial. During the investigation they were on their normal diet.

The children received no treatment during a preliminary period of 14 days. They were weighed at the beginning and at the end of this period. They were then sent to the pharmacist, who selected at random a paper from an envelope. This stated whether the child was initially to be given phenmetrazine or dummy tablets.* Sufficient tablets for 28 days' use were dispensed. The dose of phenmetrazine was 25 mg. in the morning and midday for children aged 8 years and over, and 12.5 at the same times for children under 8. At the end of the 28 days the child was weighed and a further supply of tablets was prescribed. The second set of tablets was the opposite—active or dummy—to that which the child had received previously, so that each child acted as his own control. At the end of the second period of 28 days the child was again weighed and then took no further part in the investigation. The children and their parents did not know that the tablets were different, and only the pharmacist knew which tablets the child received until after the investigation was completed and the results had been tabulated.

Eleven children did not complete the full course and are not included in the series. This was because of two main reasons. (1) Some children failed to return for weighing at exactly the right time because of holidays or for other domestic reasons. Many of these children attended a week later, but as they had been without tablets for a week they could not be included in the trial. (2) Some children had an illness, such as measles or tonsillitis, which probably affected their appetite.

*The phenmetrazine and dummy tablets were kindly supplied by Boehringer Products division of Pfizer Ltd.

Results

The results of the experiment are shown in the Table. Twenty-one children completed the trial. During the first two weeks the children gained between ½ and 5 lb. (227 and 2,270 g.) in weight, with an average of about 2 lb. (907 g.). While receiving phenmetrazine 18 children

Result of Double-blind Controlled Trial of Phenmetrazine

Case No.	Weight Gain During Preliminary Two Weeks (in lb.)	Weight Gained or Lost While Receiving Phenmetrazine (in lb.)	Weight Gained or Lost While Receiving inert Tablets (in lb.)
1	+1	−½	+1½
2	+1	−1	+2
3	+3	Nil	+1
4	+2	−7	−1
5	+3½	−4	+1
6	+3	−2½	Nil
7	+1	−8	+1½
8	+½	−5	+3
9	+1½	−2½	+3½
10	+½	−7½	+1½
11	+3	−4½	−1½
12	+1	−½	+4
13	+1	−3	+2
14	+½	−4	+1½
15	+½	−6	+1
16	+3	−3	+2
17	+3	Nil	+3
18	+1	−6	+1
19	+2½	−1½	Nil
20	+5	−2	+3
21	+1	+4	+5

1 lb. = 454 g.

lost between ½ and 8 lb. (227 and 3,630 g.) with an average of 4 lb. (1,815 g.), two children remained stationary, and one child gained 4 lb. (1,815 g.). While receiving the dummy tablets 17 children gained from 1 to 5 lb. (454 to 2,270 g.) with an average of 2 lb. (907 g.), two remained stationary, and two lost 1 and 1½ lb. (450 and 680 g.) respectively. On studying the figures it will be seen that in every case phenmetrazine was more effective than the dummy tablet. Even the children who did not lose weight while receiving the drug gained more while they were not receiving it; while all the children who did not gain weight while on the placebo lost considerably while taking phenmetrazine.

Only four children failed to gain weight on the dummy tablets. These had gained at least 2 lb. (907 g.) during the probationary two weeks. Three of the four children happened to have the active drug first and the dummy second. These children give some indication of the way in which illicit dieting or minor ailments may have affected the outcome of the experiment.

Discussion

Phenmetrazine, in the dosage given, was a highly effective weapon againt obesity. The result of the experiment is the more remarkable when it is remembered that the children's diet was not restricted and they had been shown to be gaining weight prior to the time they received the drug. None of the children complained of any ill effects, though one child became very ill-tempered while receiving phenmetrazine, and her parents stopped giving her the drug.

Phenmetrazine is not an innocuous drug. Subacute delirium (Silverman, 1959), toxic psychosis (Bethell, 1957), and addiction (Kahan and Mullins, 1958; Evans, 1959) have all been described in adults with psychopathic personalities.

In order to discover the effect of phenmetrazine, no dieting was allowed in the experiment reported above. This does not, of course, mean that diet plays no part in the treatment of childhood obesity. On the contrary, appropriate dietetic measures should be the mainstay of treatment, and only if that fails should phenmetrazine be introduced as a useful adjuvant. No treatment apart from starvation in hospital will succeed unless the child is willing to co-operate. Indeed, as Wallgren (1959) has indicated, it may well be better in some cases for the child to remain fat than to provoke an unnecessary psychological tussle.

Summary

A double-blind controlled trial of phenmetrazine on 21 children receiving an unrestricted diet gave the following results: while receiving phenmetrazine 18 children lost weight, 2 remained stationary, and 1 gained weight. While receiving inert tablets: 17 children gained weight, 2 remained stationary, and 2 lost weight.

The potential dangers of phenmetrazine and the indications for its use are indicated.

I thank Drs. C. C. Harvey, J. Lorber, M. W. Partington, and Mr. J. Sharrard for referring cases to me; Miss C. I. Crawford, the hospital pharmacist, for her co-operation; and Professor R. S. Illingworth for referring cases and for kindly criticizing this paper.

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USE OF ^{82}Br IN DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTIC MENINGITIS

BY

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The Bromide Partition Ratio

In 1929 Walter described a method for estimating bromide levels in blood and cerebrospinal fluid (C.S.F.) and showed that in the normal subject there was a blood/C.S.F. barrier. The partition of bromide between blood and C.S.F. could be expressed as a bromide ratio,

$$\frac{\text{bromide per unit volume serum}}{\text{bromide per unit volume C.S.F.}},$$

which fell within the range 2.9 to 3.5 (mean 3.1). Walter also showed that in tuberculous meningitis and in

neurosyphilis the permeability of this barrier to bromide increased and that the ratio consequently fell.

By using a different chemical method and with slight modification of Walter's technique, Taylor *et al.* (1954) showed that in subjects "without overt disease of the nervous system" the mean bromide partition ratio was 2.6 ± S.D. 0.3 Smith *et al.* (1955). The same workers studied 66 patients with early lymphocytic meningitis. In 33 of these tuberculous meningitis was subsequently proved, and 30 of them had a bromide partition ratio of less than 1.6. Only 2 of the 33 cases of non-tuberculous lymphocytic meningitis had partition ratios of less than 1.6. The differences in the bromide ratios in the two groups were independent of any differences in the amount of protein and cells in the fluids. Other workers (Cheek, 1956; Nicol and Fawns, 1958), using this same method, have reported favourably on the differential diagnostic value of the bromide partition test in cases of non-purulent meningitis. In a series of 26 cases of early undiagnosed lymphocytic meningitis, Nicol and Fawns (1958) showed that every case subsequently confirmed as of tuberculous origin had a bromide partition ratio of less than 1.4 during the first few days of observation. There were no false-negative results.

Chemical Methods of Estimating the Bromide Partition

Serum or C.S.F. levels of bromide are normally too small to be measured accurately, and in order to estimate the bromide ratio it is necessary to administer supplementary bromide. This is usually done by the oral or intravenous routes 48 hours before the simultaneous sampling of blood and C.S.F.

Walter (1929) originally used a gold chloride method for his bromide estimations. Hunter *et al.* (1954) later showed that though the method gave reliable results for estimations of bromide in C.S.F. the figures obtained in the estimation of serum bromide were too high, substances other than bromide being present in serum and reacting with gold chloride to give the same brown colour. The iodometric titration methods originally described by van der Meulen (1931) and later modified by Hunter (1953) were found to give more reliable results. Even with such methods, however, the chemical estimation of bromide in body fluids is difficult and often laborious. Ashing, extraction, and subsequent titration of each sample is necessary. The accuracy of the estimation has been noted to vary with the concentration of bromide present and the volume of the sample available. Moreover, the method requires the standardization of a number of reagents. The procedure is time-consuming and the error of occasional single estimations is probably more than the ± 1% claimed.

We have therefore investigated the possibility of using a radioactive isotope of bromine to estimate relative bromide concentrations in blood and C.S.F. The method was found to be simple, reliable, and applicable to very small samples.

Material and Methods

The radioactive isotope used is ^{82}Br, which has a half-life of 36 hours and emits β rays of maximum energy 0.4 MeV and γ rays with energies in the range 0.55–1.47 MeV.

A dose of 50 μc. of radioactive sodium bromide is administered orally in 50 ml. of water. Forty-eight hours later a lumbar puncture is performed. The first 5 ml. of C.S.F. is taken for estimation. A 5-ml. blood sample is taken at the same time.

Equal volumes (usually 1 or 2 ml.) of serum or C.S.F. are counted in a sodium iodide, thallium-activated scintillation counter, similar to the Ekco well-type scintillation counter (serial No. N557). The counts obtained on each specimen are corrected for background and dead-time, and the ratio of these corrected counts (serum/C.S.F.) gives the bromide partition ratio.

On the assumption that the ingested material is fairly uniformly distributed and that none of it is excreted during the period of the test (which is probably never the case) it was calculated that the body would receive a total dose of 200 mr. This may be compared with a maximum permissible dose of 300 mr/week for persons *habitually* working with radioactive materials in controlled areas (Code of Practice for the Protection of Persons Exposed to Ionizing Radiations, H.M.S.O., 1957).

Results in Patients without Meningitis

Diagnostic lumbar puncture on patients without clinical evidence of meningitis gave opportunities of obtaining control data.

Our patients had various neurological disorders (cerebrovascular disease, cerebral and spinal tumours, cortical atrophy, cervical or lumbar spondylosis with neurological complications, syringomyelia, and disseminated sclerosis). In most instances the lumbar puncture was part of the procedure of myelography or air encephalography.

The bromide partition ratios were estimated in 30 such patients and varied between 1.9 and 3.7 (mean 2.6, S.D. 0.4). The ratios were independent of the protein or cell content of the fluid. In no instance were readings obtained which might invalidate the hypothesis of a blood/C.S.F. barrier to bromide in patients with non-infective neurological disorders.

Our findings confirm the existence of a blood/C.S.F. barrier for bromide in patients without meningitis and show that this barrier can readily be estimated by the use of ^{82}Br.

Results in Patients with Meningitis

In the Table are recorded some investigations on patients who presented with symptoms or signs of meningeal irritation.

The serum/C.S.F. bromide barrier, as estimated with ^{82}Br, was maintained in the five cases of non-tuberculous lymphocytic meningitis and grossly affected in two cases later proved, by C.S.F. culture and guinea-pig inoculation, to be tuberculous meningitis.

Investigations in Patients with Signs or Symptoms of Meningeal Irritation

Case No.	Age	C.S.F. Protein (mg./100 ml.)	C.S.F. Cells (per c.mm.)	C.S.F. Glucose (mg./100 ml.)	Serum/C.S.F. ^{82}Br Partition Ratio	Diagnosis
1	28	120	850	50	2·0	Benign lymphocytic meningitis
2	29	150	30	71	2·4	Subdural empyema
3	27	124	90	73	2·6	Poliomyelitis
4	25	200	2,215	41	2·3	Benign lymphocytic meningitis
5	28	90	330	62	3·3	,, ,,
6	35	104	500	37	0·9	Tuberculous meningitis
7	45	260	160	37	0·9	,, ,,

The diagnostic value of the bromide partition test is illustrated by Cases 3 and 6, described in more detail below.

Case 3.—A 27-year-old haulage contractor had developed back pain and later headache, nausea, and vomiting while shovelling gravel. He was admitted to hospital with fever (102° F.; 38.9° C.) and photophobia. He was irritable and there was marked stiffness of the neck and back. The fundi were normal. The C.S.F. contained: cells, 90/c.mm. (90% lymphocytes); protein 124 mg./100 ml.; and glucose 73 mg./100 ml. The bromide partition was 2.6. It was decided to observe him for 24 hours. Two days later he developed paresis of the hip flexors and of the muscles of the back and anterior abdominal wall. Diagnosis: acute poliomyelitis.

Case 6.—A 35-year-old Nigerian student nurse was admitted after the sudden onset of severe headache and vomiting. She was pyrexial (102° F.; 38.9° C.), photophobic, and showed marked meningism. The fundi were normal. The C.S.F. contained: cells, 500/c.mm. (all lymphocytes); protein, 104 mg./100 ml.; and glucose, 37 mg./100 ml. No organisms were seen on direct smear. The bromide partition ratio was 0.9. Anti-tuberculous therapy was started. Culture of the initial sample of C.S.F. subsequently grew acid-fast bacilli. With continued treatment the patient has become symptom-free. Eight months after the onset of the illness the bromide partition ratio was still low. Diagnosis: acute tuberculous meningitis.

Comment

Tuberculous meningitis often presents as a lymphocytic meningitis, the bacterial cause of which may remain unproved until the results of culture or guinea-pig inoculation are available. Anti-tuberculous therapy is often started in such cases, the diagnosis being based on clinical suspicion and indirect laboratory evidence. This is undoubtedly justified in view of the risks that attend delay in initiating treatment in tuberculous meningitis. On the other hand, it has been claimed that injections (for instance, streptomycin injections) given during the pre-paralytic phase of acute poliomyelitis may contribute to the development of local paralysis. The bromide partition test seems to be a useful adjunct to our diagnostic armamentarium when confronted with cases of lymphocytic meningitis of as yet undetermined aetiology.

Using a radioisotope of bromine, we have demonstrated significant lowering of the bromide partition ratio in two cases of tuberculous meningitis, while in five other cases of lymphocytic meningitis and in control subjects the ratio was not significantly altered.

The chief advantage of using radioactive bromide is the speed and simplicity of estimation of the serum/C.S.F. ratio.

Summary

A technique using oral radioactive bromine to determine the serum/C.S.F. partition ratio is described. The values obtained in five cases of non-tuberculous lymphocytic meningitis, in two cases of tuberculous lymphocytic meningitis, and in 30 controls are given.

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Medical Memoranda

Reduction of Fractures and Dislocations Without a General Anaesthetic

In a casualty department the administration of a general anaesthetic for the reduction of fractures or dislocations has a number of disadvantages. These include the need for an anaesthetist to be present, the need for the patient to wait for four hours if food or drink has been taken recently, and the delay in recovery from a general anaesthetic, during which time the patient cannot leave the hospital.

Because of these disadvantages we decided to study the possibility that most or all of these reductions can be carried out after giving an intravenous dose of a narcotic analgesic such as pethidine. For the purpose of this trial, we decided to use "pethilorfan," a proprietary preparation containing pethidine and levallorphan tartrate in the proportion of 80 to 1. It is claimed that the inclusion of a small dose of a narcotic antagonist (levallorphan tartrate) greatly reduces the respiratory-depressant effect of the pethidine, and we felt that this should be an advantage, particularly in young children and in the elderly.

TECHNIQUE

As soon as we are ready to carry out the reduction the patient is given an intravenous injection of pethilorfan. The dose is usually 2 ml. (100 mg. of pethidine + 1.25 mg. of levallorphan tartrate) but varies with the age and size of the patient, children being given one-half to three-quarters of this dose according to age. The drug is given undiluted and is injected slowly over a period of 20 seconds. The patient is told that he will become drowsy but will not fall asleep, and that a manipulation will be carried out but that he will not feel pain. It is necessary to give this explanation carefully, as otherwise some patients expect to lose consciousness and think that the injection has failed when they do not do so. It is essential to maintain the patient's co-operation throughout the procedure. We have found that the optimal time for starting the manipulation is 10 minutes after the injection or as soon as the patient becomes drowsy. After the reduction is completed, the effects of pethilorfan wear off very rapidly, and the patient can usually go home as soon as the post-reduction *x*-ray film has been taken.

We have used this technique for the treatment of 30 fractures and 9 dislocations.

Reduction was successfully carried out in 36 of these 39 patients with the use of pethilorfan alone. We noted that, even if some pain was complained of during the actual manipulation, when seen in the fracture clinic two days later the patient had no memory of this. In children, in particular, the manipulation was often completely painless. We quote the casualty officer's

Fractures		Dislocations	
Colles's fractures in adults (aged 48–83)	11	Shoulder	3
Shaft of radius and ulna in children (aged 5–14)	10	Jaw (bilateral)	1
Tibia and fibula	6	Elbow	2
Shaft of femur	2	Metacarpo-phalangeal joint of thumb	1
First phalanx of index finger	1	"Locked knee"	2

comment on the card of one child aged 7: "Fracture reduced under pethilorfan. Considerable force used during reduction with absolutely no pain; the child did not even wince."

The failures comprised one dislocation of the elbow, one fractured femur in a young and muscular man, and one case of "locked knee"; two of these were later reduced satisfactorily under a general anaesthetic.

No side-effects or complications were observed in any of the cases described above.

This technique has revolutionized our work in the casualty department. The need for an anaesthetist is much less frequent, fractures and dislocations can be reduced immediately even if the patient has recently had a meal, and patients can usually go home immediately the post-reduction *x*-ray film has been taken.

I wish to thank Mr. G. K. Rose, Consultant Orthopaedic Surgeon.

J. R. PEARSON, M.B., F.R.C.S.,
Orthopaedic Registrar, Royal Salop Infirmary, Shrewsbury, and Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry.

Diabetes Insipidus After Tuberculous Meningitis

Lorber (1958) has drawn attention to the apparent rarity of diabetes insipidus as a sequel to successfully treated tuberculous meningitis. He quoted 11 examples from the literature, and added one case of his own. Acheson and Smith (1958) refer to two cases, so that in the English literature there are only three recorded cases.

The object of this short communication is to publish another case and refer to the difficulties in management.

CASE HISTORY

A Maori child of 3 years was admitted to the Dunedin Hospital on February 25, 1956, with a two-weeks history of cough, fever, and anorexia, followed by the development of drowsiness and irritability. Three months previously the boy had been treated elsewhere for primary pulmonary tuberculosis producing collapse of the right upper lobe. No antituberculous drugs were given. The child's mother had had pulmonary tuberculosis, and a sibling had died of tuberculosis.

On examination he was drowsy and showed obvious signs of meningeal irritation. There were scattered rhonchi over the right lung.

Lumbar puncture revealed a faintly turbid fluid under pressure of 200 mm. of C.S.F.; there were 480 leucocytes/c.mm. (lymphocytes 70%, polymorphs 16%, mononuclears 14%), the protein was 160 mg./100 ml., and sugar 38 mg./100 ml. No tubercle bacilli were seen, and subsequent culture and guinea-pig inoculation were negative. Chest *x*-ray examination showed consolidation in the right upper lobe with mediastinal glandular enlargement.

The child was treated with intrathecal streptomycin, 50 mg. daily for 14 days, and on alternate days for 14 days; intramuscular streptomycin, 1 g. daily for six months; and isoniazid, 50 mg. b.d. for six months. His clinical progress was satisfactory, and when after four months he was transferred to a convalescent home he showed no abnormal physical signs.

On August 7 a further lumbar puncture showed 177 erythrocytes, 17 leucocytes (43% lymphocytes, 57% polymorphs), protein 120 mg./100 ml., sugar 60 mg., and no growth.

In October, eight months after the onset of his meningitis, symptoms of diabetes insipidus first developed. He began to drink excessively and pass large amounts of dilute urine, slept more than usual, and became suspicious in temperament. He was readmitted to hospital, and fluid-balance studies showed that his intake was up to 3.5 litres of fluid a day, and his output usually towards 3 litres. Examination of the urine showed nothing abnormal except for a specific gravity constantly about 1002. He was not obese or unduly somnolent at this stage, and in all other respects he was entirely well. A skull *x*-ray film was normal.

At first he showed a dramatic response to vasopressin ("pitressin") tannate injections, a dosage of 0.25 ml. intramuscularly reducing his intake and output to about 1 litre for two to three days, with a corresponding rise in specific gravity. However, he soon became tolerant of this dosage, and was eventually stabilized on 0.5 ml. twice weekly, but never was there smooth control or a constant response to an injection.

In December he was seen at the Christchurch Hospital, and on a dosage of vasopressin tannate, 1 ml. twice weekly, his urine output ranged from 1,500 to 400 ml., with specific gravities from 1001 to 1026.

In July, 1958, he was readmitted because his injections were painful and not adequately controlling his thirst. His vasopressin was stopped for 14 days, during which his fluid intake ranged from 1,800 to 3,350 ml., and the specific gravity of his urine was uniformly low. With recommencement of vasopressin injections and later vasopressin snuff, there was an immediate fall in his fluid intake. At first two snuff capsules a day controlled his symptoms, but this later had to be increased to four capsules a day. This led to the complication of infection in the nose, which responded to local antibacterial treatment. The child was able to return to school, and though control was never ideal, his mother considered that the snuff achieved a better result than the injections.

COMMENT

The clinical diagnosis of diabetes insipidus and the tuberculous aetiology in this patient are beyond question. A response to vasopressin therapy has been achieved, but management in a child of 5 years (the youngest on record) has proved a difficult problem. Injections of vasopressin gave a prompt effect, but its duration was unpredictable and the injections were often painful. The use of vasopressin snuff has resulted in fair control, but at the cost of high dosage and nasal infection. Three of the recorded cases have apparently recovered within two and a half years of the onset of diabetes, so that an optimistic prognosis may yet be justified.

I thank Dr. Murray McGeorge for permission to publish this case, and Miss Margaret Watson for her secretarial assistance.

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Now that the processing of paprika is carried out by machinery, toxomycosis, a disease similar to pulmonary tuberculosis, has disappeared from Szeged, the famous paprika centre in southern Hungary. Known locally as the "Szeged illness," it was caused by the inhalation of spores of certain paprika moulds and hot pepper dust during the splitting of ripe paprika, which used to be done by women and girls on the Szeged paprika farms. (Hungarian News Service.)

Reviews

SKIN CANCER

Cancer of the Skin. By John C. Belisario, C.B.E., E.D., M.D., Ch.M., D.D.M. (Pp. 321+xvii; illustrated. 50s.) London: Butterworth and Co. (Publishers) Ltd. 1959.

Primary skin cancer is much more common in Australia than it is in the United Kingdom and most other countries. For these reasons Dr. Belisario has a particularly wide clinical experience of primary carcinomas of the skin, and the first part of his book is devoted to this subject. In discussing aetiology and prevalence he follows the accepted view that cutaneous carcinoma in most cases depends on the degree of exposure and the susceptibility to sunlight. His table of its association with race and pigmentation, however, is not based on controlled observations, and is one of several examples where conclusions which are accepted as correct appear to have been drawn on inadequate evidence. Again, on page 15 he states: "46.5% of all cancers occurring in white men in Dallas were cancers of the skin, while in Chicago only 12.5% of all cancers in white men involved the skin. This indicates that skin cancer is less common in the north than in the south."

Although this is not a very long book, the author nevertheless aims at completeness and includes mention of other carcinogens which may be operative on the skin surface. In this section it is curious that he should quote carcinoma as arising on lupus vulgaris in 0.5% of cases, but in 6 to 12% of cases of lupus erythematosus. Most dermatologists in Europe would consider carcinoma more likely in lupus vulgaris. There is an interesting chapter on skin manifestations associated with internal malignancy. This group of conditions, which includes acanthosis nigricans, Peutz's syndrome, and generalized pruritus, is of considerable interest to the general physician as well as to the dermatologist.

The radiotherapy of primary carcinoma of the skin, particularly of smaller lesions, is often undertaken by dermatologists in Australia even as an office procedure. In the United Kingdom most dermatologists prefer to ask the radiologist to deal with these cases. The use of radioactive isotopes in superficial therapy is dealt with very briefly.

During the last six years Dr. Belisario has treated most early carcinomas and some advanced lesions by curettage followed by the local application of podophyllin. The treatment of carcinomas by local application of antimitotic agents has of course often been attempted, but in the past results have been too variable for these methods to be widely adopted.

There is a section on malignant melanoma, followed by chapters on sarcoma, malignant reticulo-endothelioses, and the cutaneous manifestations of leukaemia and polycythaemia.

There are 35 closely printed pages of references in the main part of the book, followed by another two pages of more recent references in the appendix. Among the 200 illustrations in this book there are some very good pictures. A number, however, are below standard, and their inclusion is not particularly helpful. There are eight colour plates of variable quality.

F. RAY BETTLEY.

SURGICAL ANATOMY OF BACK AND LIMBS

Anatomy for Surgeons. Volume 3. *The Back and Limbs.* By W. Henry Hollinshead, Ph.D. (Pp. 901+xii; illustrated. £8 8s.) London: Cassell and Co. Ltd. 1959.

The third, and presumably last, volume of this textbook of surgical anatomy is, like its predecessors, a thoroughly detailed and scholarly work. Dr. Henry Hollinshead as professor of anatomy at the Mayo Foundation is in the most suitable possible sphere for an anatomist anxious to collaborate to the full with surgery of the first rank.

This book bears no relationship to the old-fashioned manuals of surgical anatomy designed mainly for Final or Fellowship reading. It is essentially a fully detailed textbook of descriptive anatomy, but one arranged in such a way that the surgeon in search of unfamiliar anatomical situations or unexpected variations from the normal can find exactly what he is looking for.

It is inevitable that, concerned as it is with the back and the limbs, it should be of special interest to the orthopaedic surgeon, the vascular surgeon, and the surgeon interested in peripheral-nerve work. The hand, however, is considered in as much detail as the rest of the upper limb, and the descriptions of tissue spaces, tendons and tendon sheaths, joints, vessels, and nerves are superb. The illustrations are most lucid; most of them are simple line drawings, some of them are in two colours. They are artistically most satisfying. The references lay open before the surgeon an anatomical literature with which he is not likely to be familiar; the titles of papers are given, and some of them are well calculated to stimulate curiosity. Developmental anatomy is very lucidly considered and expounded.

The book is large but strongly built, and capable of fairly easy handling on the table or even on the knee, for the pages lie open and flat in a very convenient way. It represents a very high order of the publishing art, particularly in the paper, type, and the lay-out of illustrations and tables. At eight guineas the book is expensive, for presumably the three volumes must cost 24 guineas—not necessarily too costly for its value, but a heavy burden for a private pocket. Medical school and hospital libraries, however, should have it on their shelves.

IAN AIRD.

MECHANISM OF CARCINOGENESIS

Ciba Foundation Symposium on Carcinogenesis Mechanisms of Action. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Maeve O'Connor, B.A. (Pp. 336+xii; illustrated. 48s.) London: J. and A. Churchill. 1959.

This volume, which reports the proceedings of a symposium organized by the Ciba Foundation, is dedicated to the memory of the late Sir Ernest Kennaway. The meeting was held in London immediately before the Seventh International Cancer Congress, and was attended by cancer research workers from nine countries, representing all the disciplines now employed in the solution of the many fundamental problems associated with carcinogenesis. In conformity with the modern trend, approximately two-thirds of the eighteen papers dealt with the mechanism of carcinogenesis. Three of these were concerned with co-carcinogenesis; others presented the immunological, pharmacological, and endocrinological aspects, while the mechanism of bladder-cancer induction, the relation of

protein binding to hydrocarbon carcinogenesis, and the loss of specific cell antigens were also discussed. More directly related to the carcinogenic agents themselves were papers on the induction of cancer by plastic films, by viruses, metals, and cell-free extracts, and by ionizing radiations. Ample time was allowed for free and critical discussions, whose high standard could be maintained only by limiting the number of those taking part.

The editors hope that this complete record of the proceedings will afford "the pleasure of vicarious participation" to all those working in cancer research who could not be invited to the meeting. The reporting is so accurate that the editors can rest assured that their hopes will be realized.

GEOFFREY HADFIELD.

BIOCHEMISTRY AND MEDICINE

Biochemistry in Relation to Medicine. By C. W. Carter, M.A., B.M., B.Ch., R. V. Coxon, M.D., D.Phil., D. S. Parsons, M.A., D.M., and R. H. S. Thompson, M.A., B.Sc., D.M. Third edition. (Pp. 628+xiii; illustrated. 50s.) London, New York, Toronto: Longmans, Green and Co. 1959.

The appearance of a third edition of this popular work exactly 10 years after the first edition indicates a continuing demand and a healthy growth of the subject.

The latest edition has been changed more radically than the second, and the subject matter has been largely recast. The practical exercises are now omitted, but new sections have been added on endocrine control of metabolism, reproduction, the thyroid, the adrenal glands, and nutrition, and many of the earlier sections have been considerably expanded. Dr. Carter and Professor Thompson are now joined as co-authors by Dr. Coxon and Dr. Parsons. The two new contributors are from Oxford University, so that the original orientation of the book towards the Honours Physiology course is retained. There is an overall increase of size of some one hundred pages.

The previous high standard of writing has been maintained, and all sections may be read with great interest by those concerned with either clinical biochemistry or more basic biochemical work with a physiological or pathological bias. Though it is addressed primarily to medical students, the book will doubtless have a wide circulation among clinical and pre-clinical biochemists, pathologists, and scientifically minded clinicians. It can be cordially recommended to all these classes of reader.

N. F. MACLAGAN.

THE CAROTID BODY AND SINUS

The Comparative Morphology of the Carotid Body and Carotid Sinus. By William Edgar Adams, D.Sc., Ph.D., B.Med.Sc., B.M., Ch.B., F.A.Z. (Pp. 272+xviii; illustrated. 80s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

The aim of this volume is to give a comprehensive review in English of the comparative morphology of the carotid body and sinus. The review includes a historical survey not only of the anatomy, but also of the physiology, of what the author describes as the "carotid fork." In Part I a detailed account of the macroscopical and microscopical structure of the human carotid body and sinus is given, followed by a review of the structure in many orders of mammals. Part II deals with the carotid mechanism in birds, reptiles, and amphibia. In this section the question of the presence in elasmobranch fishes of a structure homologous to the carotid body is discussed. Professor Adams comes to the conclusion that the mammalian carotid body is not functionally homologous with the "axillary heart" of elasmobranchs. We are, indeed, indebted to Adams for giving us such an extensive bibliography of the carotid gland and sinus. The book will be of immense value to all who are interested in this small but important structure.

W. J. HAMILTON.

TOXICOLOGY

Handbook of Toxicology. Prepared under the direction of the Committee on the Handbook of Biological Data, Division of Biology and Agriculture, National Academy of Sciences. Volume III, *Insecticides.* (Pp. 854+xxv. 98s.) Volume IV, *Tranquillizers.* (Pp. 120+viii. 28s.) Volume V, *Fungicides.* (Pp. 242+ix. 38s. 6d.) Philadelphia, London: W. B. Saunders Company. 1959.

These volumes from a series of handbooks of biological data differ considerably in weight, format, and quality of their contents.

Volume III, by far the most comprehensive, has sections on 160 individual insecticides, 12 other sections on groups of compounds, and a few on such topics as "Resistance" and "Oviposition Inhibitors for *Musca domestica.*" The amount of information on a well-known compound like D.D.T. is enormous, though the non-chemist will have difficulty in locating this substance in the table of contents, as popular and chemical names are used indiscriminately. There are 3,404 neatly tabulated references, and two indexes to sections and not pages.

Volume IV gives information on 26 drugs used as tranquillizers, supplied by experts from seven U.S. drug manufacturers. Data on their chemical and physical properties, pharmacological action, clinical uses, and toxicity, are set out in a standard way, with references after each section. While one is amazed to note that so many compounds claiming to share similar therapeutic virtues can all find a market, the authors are to be complimented on the fact that the section on toxicity is almost invariably longer than that on clinical uses.

Volume V does little more than list 196 compounds with fungicidal activity, which sometimes amounts only to an ability to inhibit spore germination in the test-tube. Well-known fungicides like methyl and ethyl mercury compounds or the trialkyltin compounds are not mentioned, though vitamin B_6 earns a place. The references are massed at the end and run continuously, making a search tedious. This is made even more irritating by the fact that only about one-third refer to scientific papers; the rest are references to unpublished reports or standard textbooks. A list of patent numbers is given.

The usefulness of books of this kind is questionable unless they are in loose-leaf form where additions can be made at intervals. While one may marvel at the industry that went to compile the volume on insecticides, it is of no use to anyone looking for an answer to a simple question such as a substance good for killing ants. The volume on tranquillizers is undoubtedly the most useful,

but it is likely to become out of date before Volume III. The volume on fungicides does no credit to the series.

The sponsors of these handbooks might consider whether it would not be better to give the titles of the references quoted and reduce the text under each heading.

J. M. BARNES.

GOOD REFRESHER COURSES

The Year Book of Medicine, 1958–1959. Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D. (Pp. 782; illustrated. 57s.) Chicago: Year Book Publishers, Inc. London: Interscience Publications Ltd. 1958.

The Year Book of Drug Therapy, 1958–1959. Edited by Harry Beckman, M.D. (Pp. 569; illustrated. 57s.) Chicago: Year Book Publishers, Inc. London: Interscience Publications Ltd. 1959.

Most of us have the impression that we work much harder and have far less time for reading than any preceding generation of physicians. This may be a complete delusion, but it is certainly true that we have far more to read than our predecessors, and it would be a full-time job for anyone to keep up even a nodding acquaintance with the enormous literature which rapidly accumulates round each new medical discovery. Thus year books of this type, in which what is really important in the world's vast medical literature is selected and abstracted by experts, are becoming more and more popular, and serve as valuable refresher courses for us all in current advances in medicine and therapeutics.

The 1958–9 *Year Book of Medicine* and *Year Book of Drug Therapy* maintain the high standard of their predecessors; there can be few important papers published in the past year which do not receive attention, and the distinguished editors of both books have been most successful in describing the essential features of each piece of work reviewed in concise and simple language. Though American literature, perhaps rightly, receives pride of place, the selection of papers for abstraction is refreshingly cosmopolitan; in the *Year Book of Drug Therapy*, for example, a précis has been made of 493 articles from 23 countries and 108 journals. As the editor must have perused and discarded a far greater number of papers, one is left astounded by his industry. Both year books are excellent and can be unreservedly recommended.

D. M. DUNLOP.

"Psychiatry," says Professor E. H. Ackerknecht, "has always been in many ways the most human and most interesting of the medical sciences," and he is capable not only of saying it but of demonstrating it as well. His book *A Short History of Psychiatry* covers the subject from its Graeco-Roman beginnings, through the Renaissance, the seventeenth and eighteenth centuries, and the French School in the nineteenth century, to the neurologists who fathered modern psychotherapy, to the work of Pavlov, and to what he calls "the newer somato-empirical treatment methods" of the present day. He has one of those very clear "signpost" minds that are invaluable to anyone making a first acquaintance with, or revising, a complicated subject. His style, even in translation, is easily read, trenchant, and often witty, and is enlivened by flashes of what his opponents would call prejudice and his sympathizers a refusal to disguise what, in his opinion, the emperor's new clothes are made of. (Hafner Publishing Company, London; 93+vi pp.; 9 plates, index, 25s.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Mirage of Health. Utopias, Progress, and Biological Change. By René Dubos. (Pp. 221. 21s.) London: George Allen and Unwin, Ltd. 1960.

Atopic Cataract. By Emanuel Rosen, M.D. (Pp. 102+xiv; illustrated. 46s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Eritroenzimopatie ed Anemie Emolitiche. By Ugo Carcassi. (Pp. 376; illustrated. L. 3,000.) Pisa: Edizioni "Omnia Medica." 1959.

The Pane of Glass. By John Bartlow Martin. (Pp. 397+xii. 30s.) London: Victor Gollancz, Ltd. 1959.

Freud. The Mind of the Moralist. By Philip Rieff. (Pp. 397+xvi. 30s.) London: Victor Gollancz, Ltd. 1960.

Osteochondritis Dissecans. Loose Bodies in Joints: Etiology, Pathology, Treatment. By I. S. Smillie, O.B.E., Ch.M., F.R.C.S.(Ed.), F.R.F.P.S. (Pp. 224+viii; illustrated. 60s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

The Triumph of Surgery. By Jürgen Thorwald. (Pp. 483. 25s.) London: Thames and Hudson. 1960.

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CLOSTRIDIUM WELCHII FOOD-POISONING

In 1958[1] there were 69 general outbreaks, 10 family outbreaks, and 9 sporadic cases making a total of 88 incidents of *Clostridium welchii* food-poisoning. The numbers were 93 in 1957,[2] 77 in 1956,[3] 90 in 1955,[4] and a smaller number in the years 1954[5] and 1953,[6] when more was being learnt about this type of food-poisoning. Gradually pathologists have included a search for the organism in routine stool samples from patients with diarrhoea for which no cause has been found, and in food suspected to have caused food-poisoning.

As usual, almost all the outbreaks recorded in 1958 were associated with meat, and the meat had invariably been cooked some hours or even a day or more ahead of requirements. The report for that year makes the following comment: "There is so far no sign that caterers are changing cooking methods in order to reduce the risk of food-poisoning due to *Cl. welchii*." The same report shows that, in common with the other types of food-poisoning, there is a high incidence of *Cl. welchii* in school and works canteens and also in hospitals and other institutions. In certain areas of London, however, where local authorities have issued recommendations or even orders to school canteens that all meat must be cooked on the day that it is required, the incidence of *Cl. welchii* food-poisoning has dropped to a very low level, or has been obliterated altogether.

Strains of *Cl. welchii* causing food-poisoning have been classified as type A[7], though they differ from the usual type-A strains in several characteristics, the most important of which is that the spores survive 1 to 4 hours' boiling in contrast with those of the classical type-A strains causing gas gangrene, which are predominantly killed at temperatures slightly below boiling. They differ also in producing little demonstrable alpha toxin, no theta toxin, and therefore a faint zone only or no haemolysis at all on horse-blood agar. The organism is fairly widespread in nature, occurring in stools of 2 to 5% of normal human beings, and also in animal stools, the percentage varying according to species; in addition it has been isolated from a high proportion of blow-flies. As to meat, the organism has been isolated from up to 25% of raw meat samples from carcasses, and up to 10% of samples taken from frozen boneless meat.[7 8]

Cl. welchii food-poisoning is recognized easily by its symptomatology and in particular by the fact that the predominant symptom is diarrhoea with abdominal pain, rarely accompanied by vomiting, though the patient may feel nausea. Pyrexia seldom occurs, and symptoms last for 12 to 24 hours. The incubation period varies between 9 and 23 hours; the organism may be isolated from a high proportion of patients when samples are taken early after the onset of symptoms, while after about two weeks it may be isolated from approximately 50% of stool samples. Death is rare, and usually only in the elderly or patients who are already ill from some other cause.

It will be seen that the incubation period resembles that of an infection, but the symptoms are those of an intoxication. Human volunteers have failed to respond to bacteria-free filtrates of cultures prepared from food-poisoning strains, yet the disease can be reproduced readily in human volunteers by ingesting the organism actively growing in meat or soup.[7 9] There is no proof, therefore, that the alpha toxin or any other known toxin is responsible for the diarrhoea. The typical symptoms, combined with a history of taking boiled, stewed, steamed, braised, and more rarely roast meat, cooked ahead of requirements, with casual storage at warm atmospheric temperatures, should immediately suggest *Cl. welchii* food-poisoning.

Meat hygiene as at present practised is inadequate to prevent the spread of the organisms from animal, fly, or human excreta to meatstuffs. The spores are likely to survive for long periods in soil and dust,[10] in clothes, and in the environment generally not only of the kitchen but of abattoirs, markets, and retail shops. Therefore prevention must be concerned far more with care over cooking and storage than with the human faecal excretor; exclusion of carriers will do little to help the situation when the organism pours in from other sources. As a general rule meat, whether as cuts or in pies or stews, should be thoroughly cooked and eaten hot; if this is impossible, it should be cooled rapidly within 1½ hours of cooking and refrigerated until required. In any event, there should be the shortest possible time between cooking and eating to limit the number of organisms. Small numbers of spores and vegetative

[1] Report on Food Poisoning in England and Wales, *Monthly Bull. Minist. Hlth Lab. Serv.*, 1959, **18**, 169.
[2] —— ibid., 1958, **17**, 252.
[3] —— ibid., 1957, **16**, 233.
[4] —— ibid., 1956, **15**, 263.
[5] —— ibid., 1955, **14**, 203.
[6] —— ibid., 1954, **13**, 12.
[7] Hobbs, B. C., Smith, M. E., Oakley, C. L., Warrack, G. H., and Cruickshank, J. C., *J. Hyg. (Lond.)*, 1953, **51**, 75.
[8] —— and Greenwood Wilson, J., *Monthly Bull. Minist. Hlth Lab. Serv.*, 1959, **18**, 198.
[9] Dische, F. E., and Elek, S. D., *Lancet*, 1957, **2**, 71.
[10] McKillop, E. J., *J. Hyg. (Lond.)*, 1959, **57**, 31.
[11] Hobbs, B. C., *Bact. Proc.*, 1957, p. 14.

cells will be harmless; it is only when the organism has been allowed to proliferate that trouble will occur.

Delay in the distribution of meat sliced after cooking creates problems in institutions. To be safe it must be maintained either in the cold or at a temperature above 60° C. (140° F.) between slicing and distribution. The temperature of sliced meat maintained on top of a hot plate container at about 40° to 50° C. (100° to 120° F.) has proved to be ideal for the growth of *Cl. welchii*, and considerable multiplication can occur in two to three hours.[11] Safety measures may also depend on the size and the shape of the joint, for large masses of meat when rolled are not easily penetrated by heat and they are also slower to cool. Therefore, the size of the individual cuts is best limited to 6 lb. (2.7 kg.). It has been difficult to ascertain the precise temperature at which the spores are destroyed because it has so far been impossible to obtain a regular supply of spores in laboratory cultures, but experiments have shown that it is about 110° C. (230° F.). The time for which this temperature should be applied will depend on the size of the block of meat and the site of contamination. For minces, meat should be minced when raw and eaten freshly cooked; stockpots are a hazard, and the same chopping-board should not be used for both raw and cooked meat. Pressure cooking must be considered one of the safest measures aginst the survival of spores.

CHANGING SHAPES

Artists find inspiration in the infinite diversity of God's creatures, but scientists have, naturally enough, a desire to classify mankind tidily into groups and sub-groups. Medicine, having with some difficulty discarded the rigid division of physical constitution into the phlegmatic and choleric types, was not easily persuaded that subsequent attempts at classification had validity, much less any importance for practising clinicians. Renewed interest was aroused by the publication of the English translation of Kretschmer's book *Physique and Character*[1] in 1936, with its relation of physical types—circular, muscular, and linear—to specific mental diseases.

W. H. Sheldon and his colleagues in 1940[2] described a new method of "somatotyping" by photography, with their now famous division of mankind into endomorphs, mesomorphs, and ectomorphs. They added a touch of objectivity to their examination of the photographs by scoring the individual qualities of roundness, muscularity, and linearity on a seven-points scale. In a later book[3] they attempted to relate this classification to varieties of human temperament. This work was less successful: there was no attempt at objective measurement, no discussion of the effects of environment, and the temperamental and behavioural descriptions were often naïve. One critic wrote,[4] "the Sheldonian labels do not describe the contents of the luggage nor do they indicate its destination." Some attention was paid in 1944 to a book by G. Draper (a fine physician on the staff of the Presbyterian Hospital, New York, who died last year), C. W. Dupertuis, and J. L. Caughey.[5] Interesting as the book was, the accuracy of its measurements and descriptions has been questioned.

After the war anthropometrists in many countries took up Sheldon's work and in general have confirmed the value and validity of his method of somatotyping. In Great Britain R. W. Parnell and J. M. Tanner have been foremost in these studies and have published a series of well-known papers.[6–14] Both have been concerned with providing objective support for photographic somatotyping. By soft-tissue radiography Tanner[13] measures the width of bone and muscle in the limbs, and estimates fat by subtracting these measurements from the overall width of the limb. He also employs other measurements—such as the difference between the bi-acromial and bi-iliac diameters in men and women as an index of androgyny.

Parnell has sought to improve the definition of the phenotype by providing a series of routine measurements which can be quickly made. These include measurement of fat at three sites by skin-fold calliper, measurement of bone width at the condyles of humerus and femur, measurement of muscle width at biceps and calf, and measurement of height and weight. On a new type of chart, M4, based on the assumption that a rating of 4 in Muscularity will bear a constant proportional relationship to stature, the measurements can be converted into the 1–7 grading for fat (F), muscularity (M), and linearity (L). Parnell's somatocharts for showing distribution of large numbers of phenotypes, an equilateral triangle with three diagonals, M at the north, F at the south-east, and L at the south-west, are easy on the eye and on the mind. In his recent book *Behaviour and*

[1] Kretschmer, E., *Physique and Character*, 1936, London.
[2] Sheldon, W. H., Stevens, S. S., and Tucker, W. B., *The Varieties of Human Physique*, 1940, New York and London.
[3] Sheldon, W. H., and Stevens, S. S., *The Varieties of Temperament*, 1942, New York and London.
[4] Hubble, D., *Horizon*, 1946, **14**, 84, 345.
[5] Draper, G., Dupertuis, C. W., and Caughey, J. L., *Human Constitution in Clinical Medicine*, 1944.
[6] Parnell, R. W., *Lancet*, 1951, **1**, 731.
[7] —— *Brit. med. J.*, 1953, **2**, 472.
[8] —— ibid., 1954, **2**, 491.
[9] —— ibid., 1957, **1**, 1485.
[10] —— and Skottowe, I., *Lancet*, 1957, **1**, 206.
[11] Tanner, J. M., ibid., 1951, **1**, 574.
[12] —— ibid., 1952, **2**, 405.
[13] —— Healy, M. J. R., Whitehouse, R. H., and Edgson, A. C., *J. Endocr.*, 1959, **19**, 87.
[14] Lister, J., and Tanner, J. M., *Lancet*, 1955, **2**, 1002.
[15] Parnell, R. W., *Behaviour and Physique*, 1958, London.
[16] Spain, D. M., Brades, V. A., and Huss, G., *Ann. intern. Med.*, 1953, **38**, 254.

Physique[15] he has provided a good review of his own work and that of others in this field.

These studies have produced results of interest. Linear children, for example, are more difficult to breast-feed, more prone to emotional unrest, and are late in achieving control of the bladder. Their academic performance is, however, better both in the grammar school and the university. The Lf types (endomorphic ectomorphs, round and linear) are more disposed to mental breakdown under the age of 25, while the Lm types (mesomorphic ectomorphs, muscular and linear) are more disposed to mental illness between the ages of 25 and 34. There appears to be a shift from ectomorphy to mesomorphy as age is correlated with mental breakdown. Muscular mothers tend to be more fertile and to have an excess of boys among their children as compared with the general population.

The limitations of the method are now more sharply defined. It is difficult, and perhaps impossible, to forecast the ultimate somatotype by examining children before the growth-spurt of puberty has occurred. In some children the pattern is completely changed by an unexpected muscularity developing at puberty. Special considerations are required, also, for subjects with a wasting illness, in old age, and in the endomorphy of middle age. The original conception of an immutable somatotype, unaffected either by changes innate in the constitution or imposed by environment, has disappeared.

Physicians may well be inclined to underestimate the value of the method for clinical medicine, just as somatotypists may be disposed on occasion to exaggerate its importance. These methods cannot be of any help in individual diagnosis ; the mesomorphic young man of 20 may yet be suffering from schizophrenia despite his muscularity. But they may be of more help in prognosis—for example, the Mf male (endomorphic mesomorph) with schizophrenia has, on the average, a much shorter stay in hospital than the Lf type. Differing responses to treatment may well be defined in differing somatotypes. Physicians will show greater interest in somatotyping when the mechanism of the associations with disease are understood. If, for example, as D. M. Spain and his colleagues[16] showed, there is a relationship between mesomorphy and coronary atherosclerosis, is there a disposition to a disorder of fat metabolism in mesomorphs and what is the reason for it? A limitation of somatotyping in another field is shown by the fact that Mf men have a disposition either to delinquency or to material and military success ; if this shows the difficulty of social prognosis by somatotyping, it is also a useful reminder that environment plays its part in social achievement. There may be reasons to qualify Parnell's opinion that the "influence of somatotype on personality is strong," but there can be no doubt that the patient and intelligent work of Parnell, Tanner, and their colleagues has already produced conclusions of value for medicine, psychology, and sociology.

ANTIBIOTICS REVIEWED

The number of antibiotics now available is so great and steadily increasing that it is difficult for the clinician to keep himself informed about the scientific basis of their use in human disease. He is likely to be helped in this difficulty by the January, 1960, issue of the *British Medical Bulletin*, entitled "Antibiotics in Medicine." The contributions have been well chosen to keep a just balance between laboratory and clinical studies. Though these have given definitive answers to some questions, there are many practical problems upon which it is impossible to dogmatize and in which action must therefore be based on assessment of such evidence as is available. Profesor L. P. Garrod, the Scientific Editor, remarks in his preface that much of this evidence is to be found only in original papers, and that it is the aim of this issue to make such evidence conveniently available to the reader.

One of the most annoying obstacles to the acquisition and retention of clear ideas about the nature, properties, and uses of antibiotics is the confusing nomenclature which has grown up around them. Even the approved non-proprietary names are in many instances not obviously informative ; and even where these names are helpful in indicating chemical relationships, as in the tetracycline group, proprietary names, usually unrelated to the approved names or to each other, seem designed to make it as difficult as possible for the busy practitioner to keep his thoughts clear. Unfortunately, classification of antibiotics on a chemical basis is difficult, and as yet unsatisfactory ; E. P. Abraham and G. G. F. Newton divide them into three rather broadly defined chemical groups, and still have to leave a heading for miscellaneous antibiotics which fall into none of these. Even so, this chemical grouping does not correspond in any convenient way with biological facts. For instance, the group classified chemically as "derivable from amino-acids or similar units" includes antibiotics as varied in their origins and in their medical applications as cycloserine, penicillin, chloramphenicol, and polymyxin. Comparison of this chemical grouping with the table of sensitivity of pathogenic bacteria to antibiotics given by L. P. Garrod and E. F. Scowen illustrates well the present deficiencies of chemico-biological correlation. Fuller knowledge will undoubtedly remedy this, and already much is known.

The contribution by E. F. Gale on the nature of the selective toxicity of antibiotics summarizes current knowledge of the specific chemical mechanisms by which antibiotics act. In passing, it gives some fascinating sidelights on the biology of bacteria ; the cell wall is obviously important to a coccus within which the osmotic pressure may be as high as 25 atmospheres. M. R. Pollock discusses the mechanisms by which

organisms may acquire resistance to antibiotics and the heritability of drug resistance. This contribution, and that by B. W. Lacey on combined therapy, show that, though methods (discussed by J. W. Crofton) have been evolved more or less empirically by which the emergence of drug-resistant bacilli during prolonged treatment of tuberculosis may be avoided, it is unfortunately not to be assumed that methods similar to those found effective in this infection will necessarily be effective in other infections—for example, with staphylococci. E. J. L. Lowbury deals with the practical problems of the increase in resistant pathogens in hospitals which accompanies the widespread use of antibiotics, one of the most important practical problems in hospitals to-day; after discussing various policies in the use of antibiotics designed to mitigate this menace, he concludes that probably the most important measure is the attempt to prevent cross-infection. Other contributions from the laboratory side are on the control of antibiotic therapy, the pharmacology of antibiotics, and the laboratory uses of antibiotics; and from the clinical side are on the treatment of bacterial endocarditis, the preventive use of antibiotics in medicine and in surgery, and the dangers of antibiotic treatment. Finally there is a brief description by A. H. Campbell of the immensely laborious process by which the search for new antibiotics is being continued.

Only a remarkably well informed person could fail to learn something from this valuable collection of summarized statements of the current position. The average clinician reading it will be reminded continually of gaps in his reading, and will be greatly assisted towards comprehension of what he is doing when he prescribes an antibiotic.

RENAL RISKS OF PHENACETIN

Necrosis of the renal papillae (necrotizing renal papillitis) in which the necrotic papillae can be seen to stand out as pale infarct-like areas was first described in 1877 by von Friedreich.[1] Since then occasional cases have been published, and in a recent review D. Swartz and J. Hoogstraten[2] add seven cases of their own. Most cases have been associated with diabetes mellitus or the pyelonephritis of urinary obstruction, and E. E. Mandel[3] found that only 10% of 180 cases published up to January, 1953, showed no evidence of this association. In recent years further reports of cases with diabetes or obstruction of the urinary tract have been published.

In 22 out of 30 such cases O. Spühler and H. U. Zollinger[4] found macroscopic or microscopic evidence of papillary necrosis as part of the picture of a true chronic interstitial nephritis, and many of the patients had taken much phenacetin over many years. This report caused N. J. Nissen and colleagues[5] at the Frederiksberg Hospital, Copenhagen, to study 42 patients (39 women) who had for long consumed phenacetin in doses of up to 1.5 g. a day. In 12 cases papillary necrosis was found—in 10 by post-mortem examination and in 2 by microscopy of papillae voided in the urine. This lesion was found in only two other patients who came to necropsy in the same period—the cause being diabetes mellitus (plus urinary obstruction in one of them). Symptomless impaired renal function was found in 16 out of 23 patients who had taken phenacetin to excess. S. Moeschlin[6] reported 57 cases of chronic phenacetin abuse out of 2,400 admissions. Nine had evidence of chronic interstitial nephritis and four died of it. The most recent report is that of S. E. Moolten and I. B. Smith,[7] who described a fatal case in a woman of 34 who had consumed well over 20,000 tablets containing phenacetin in 5½ years. Necropsy revealed changes similar to those described by Spühler and Zollinger.

Direct proof that phenacetin can cause renal damage is hard to obtain. Animal experiments have so far failed to produce the lesions of papillary necrosis thought to be typical of damage by phenacetin. Provocation tests have been performed on 11 patients by B. Harvald, F. Valdorf-Hansen, and A. Nielsen,[8] who found a significant rise in the Addis count of red cells and leucocytes in the 12-hourly specimens of urine of patients taking a pharmaceutical preparation of phenacetin which contained acetic 4-chloranilide as a contaminant.

Phenacetin has been taken for many years, but until recently its only known toxic effect was methaemoglobinaemia, showing as a muddy complexion. This may be because the lesions now described are due to a contaminant, acetic 4-chloranilide, which was not present in the phenacetin originally made from 4-nitrophenol. Phenacetin is now prepared from 4-nitrochlorbenzol and contains acetic 4-chloranilide as a by-product. In the tests carried out by Harvald and colleagues an increase in the Addis counts did occur in patients receiving pure phenacetin, but the deviation from normal figures was not significant. A further possibility is that the effect may have been mediated by methaemoglobin formed by the drug. Points supporting the incrimination of phenacetin are that the distribution geographically and in time of the increase in cases of chronic interstitial nephritis corresponds to that of the increase of preparations containing phenacetin, and also that there is a positive correlation between consumption of these preparations and impaired renal function, evidence of renal damage being commoner in phenacetin addicts than in others. A rare but more acute type of renal damage caused by small doses of phenacetin has been reported by B. MacGibbon and colleagues.[9] Red cells with adsorbed phenacetin can act an an antigen, and "autoantibodies" may then be formed which cause haemolysis. Acute oliguric renal failure may result.

Proprietary analgesic tablets are widely used, and as they may contain up to 50% of phenacetin a dose of 4 or 5 tablets a day may easily mean an intake of 1 g. Phenacetin is peculiar in that it can itself cause headache, and it is its continued use and not its withdrawal which

[1] von Friedreich, N., *Virchows Arch. path. Anat.*, 1877, **69**, 308.
[2] Swartz, D., and Hoogstraten, J., *Brit. J. Urol.*, 1959, **31**, 419.
[3] Mandel, E. E., *Arch. intern. Med.*, 1953, **91**, 417.
[4] Spühler, O., and Zollinger, H. U., *Klin. Med. (Wien)*, 1953, **151**, 1.
[5] Lindeneg, O., Fischer, S., Pedersen, J., and Nissen, N. J., *Acta med. scand.*, 1959, **165**, 321.
[6] Moeschlin, S., *Schweiz. med. Wschr.*, 1957, **87**, 123.
[7] Moolten, S. E., and Smith, I. B., *Amer. J. med.*, 1960, **28**, 127.
[8] Harvald, B., Valdorf-Hansen, F., and Nielsen, A., *Lancet*, 1960, **1**, 303.
[9] MacGibbon, B., Loughridge, L., Hourihane, D. O'B., and Boyd, D. W., ibid., 1960, **1**, 7.

compels the patient to take more. The evidence that overdosage with phenacetin can cause chronic renal damage is strong though partly circumstantial, but when combined with the, admittedly rare, risk of damage from hypersensitivity reactions it suggests that phenacetin may have to be added to the lengthening list of beneficial drugs known to cause damage to patients who are specially sensitive or who take too much of it for too long.

BOYS ON PROBATION

With the collaboration of the staffs of certain Glasgow schools D. H. Stott, of the university department of psychology, has been studying boys placed on probation in the city during the year 1957. In a first interim report, issued in July, 1958, figures were given to show the close relationship between delinquency and other signs of maladjustment, as measured by the Bristol Social Adjustment Guides, which were designed to give a picture of the child's behaviour and to help in the detection of emotional instability. The guides seek to measure attitudes to teachers, to school work, to games and play, and to other children by scoring such qualities as withdrawal, depression, anxiety for affection, hostility to adults, and restlessness.

In a second report[1] the implications of this relationship between delinquency and other sorts of disturbed behaviour have been examined. Delinquency was found to be more prevalent in certain quarters of the city. If the theory of social infection of ordinary boys is substantially true, the probationers living in delinquency-prone localities might be expected to include a larger proportion of well-adjusted boys, but the average "maladjustment score" of probationers turned out to be surprisingly similar for areas of high and low delinquency; the probationers from the "black spots" were every bit as maladjusted as those in the "white patches." Two salient features have to be reconciled; on the one hand the Glasgow probationers included about six times as many maladjusted boys as the non-delinquent controls, while, on the other, delinquency tended to be concentrated in certain areas. Further investigation showed that the incidence of disturbed behaviour among non-delinquents rose consistently with the amount of delinquency within the locality. Apparently it was not only delinquency which was concentrated in "black spots"; probably it would be true to say that the delinquency was not the outcome of the maladjustment, but rather part of it.

The fact that so many of the probationers showed other signs of unsettledness suggested that it might be possible, by careful observation of children's day-to-day behaviour in and out of school, to spot the delinquency-prone before they were actually led to commit offences. Stott believes that the prediction value of the Bristol guide could be much improved by selecting those items which were most characteristic of the probationers as opposed to the controls. The application of such a "short list" of criteria to the whole field of probationers and non-delinquent controls picked out nearly three-quarters of the former. Whether such a prediction instrument would be equally successful in spotting the delinquency-prone from the general population of boys awaits confirmation by further field study—a big job, only practicable by the use of a rapid preliminary sorting device. The directors of the Glasgow delinquency study would like to secure the co-operation of city teachers in carrying out an investigation along these lines.

[1] Stott, D. H., *Second Interim Report of the Glasgow Survey of Boys put on Probation during 1957*, 1959, The University, Glasgow.

RENIN AND ANTIRENIN

The release of the pressor enzyme renin from ischaemic renal tissue was first detected in dogs.[1,2] Soon afterwards[3] it was shown that the substrate for the enzyme was an α-globulin. The circulating activated peptide was known either as hypertensin or angiotonin until recently,[4] when two leading workers from different countries suggested that these terms should be dropped in favour of the hybrid angiotensin.

In the last few years various workers have investigated the site of production of renin, its physiological functions, its role in human disease, and the production of an antihormone (antirenin) which might be used therapeutically. Various sites have been suggested for the production of renin, such as the juxtaglomerular apparatus,[5] the proximal convoluted tubules,[6] and the glomeruli.[7] The most recent work,[8] employing the fluorescent-antibody technique of A. H. Coons,[9] which is the most sensitive histochemical method available for this type of work, indicates that, in the pig, renin is located in the glomeruli, probably in the epithelial cells. The method used entails the preparation of an antibody in a heterologous species, and this, after labelling with a fluorescent marker, is used to stain the tissues. These results obtained in the pig are unfortunately not applicable to other species, for the cross-reactions of the antibody are not clearly defined.[8,10]

The possibility that renin might have more than one physiological activity was suggested very soon after its pressor action had been established, when diuresis and

[1] Houssay, B. A., and Fasciolo, J. C., *Rev. Soc. argent. Biol.*, 1937, **13**, 284.
[2] Goldblatt, H., Lynch, J., Hanzal, F., and Summerville, W. D., *J. exp. Med.*, 1934, **59**, 347.
[3] Page, I. H., and Helmer, O. M., ibid., 1940, **71**, 29.
[4] Braun-Menendez, E., and Page, I. H., *Science*, 1958, **127**, 242.
[5] Goormaghtigh, N., *Proc. Soc. exp. Biol. (N.Y.)*, 1939, **42**, 688.
[6] Friedman, M., and Kaplan, A., *J. exp. Med.*, 1943, **77**, 65.
[7] Cook, W., Gordon, D. B., and Peart, W. S., *J. Physiol. (Lond.)*, 1956, **135**, 46P.
[8] Nairn, R. C., Fraser, K. B., and Chadwick, C. S., *Brit. J. exp. Path.*, 1959, **40**, 155.
[9] Coons, A. H., and Kaplan, M. H., *J. exp. Med.*, 1950, **91**, 1.
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chloruresis were observed in experimentally treated rabbits.[11] This effect on capillary permeability has since been confirmed by the observation of proteinuria in rats[12] and of serous effusions in guinea-pigs, rabbits, and rats.[13] Increased permeability of liver cells to homologous serum proteins has also been demonstrated.[14] It is not known whether this effect on permeability is due to the direct action of renin or is mediated by some other substance. Recent work suggests that adrenal cortical hormones may be implicated, for renin produces enlargement of the zona glomerulosa, at least in rats,[15] and adrenalectomy in hypertensive rats restores the blood pressure to normal.[16] It seems likely, also, that adrenal steroids may influence the secretion of renin, for the amount of renin in the contralateral kidney is reduced in rats made hypertensive by clamping one renal artery and when retention of sodium is induced by D.O.C.A.[17]

Many of the efforts to show that the renin–angiotensin mechanism has a significant role in human disease have produced negative or equivocal results. Indeed, an increase in production of renin, detected indirectly by increased activity of angiotensin in the blood, has been found only in acute hypertensive states. Thus a 20-fold increase in malignant hypertension[18] and a fivefold to tenfold increase in acute glomerulonephritis[19] have been seen. There is still no evidence that excess renin is present in chronic hypertension in man and its role in chronic experimental hypertension is still uncertain.[20]

Soon after the pressor activity of renin was discovered it was noted that the serum of rabbits injected repeatedly with dog renin contained an antihormone which is known as antirenin.[21] This substance has been studied in detail[10 22] and is formed in many species of animal, as well as man, when injected with heterologous renin. Though human anti-hog renin neutralizes the activity of renin from several other species, it does not inactivate human renin and has no effect on the blood pressure of human patients.[23 24] Attempts to overcome this species specificity were unsuccessful.[10] If this line of treatment is to be pursued, it will be essential to produce human antirenin in another species, for homologous renin is not effective.[22] The yield of renin in man is only one-fortieth of that in the hog.[25] When it is considered that the amount of renin per patient used in the human experiments[23] was derived from approximately 20 kilograms of kidney, it is unlikely that antirenin will ever play a significant part in the treatment of human hypertension. Much further work is required to establish the true roles of renin and antirenin in man.

COLLEGE OF GENERAL PRACTITIONERS

The College of General Practitioners has reached a decisive stage in its growth. It must now undergo metamorphosis or its great potentiality will remain stunted. To enable it to acquire a permanent home for its headquarters and enough money to finance its activities, the College is appealing for £1m. The sum is to be allotted roughly as follows: building and equipping of headquarters, £450,000; education, £250,000; research, £300,000. The names of some who have already generously responded are listed at p. 723.

The rapid growth of the College in the first six years of its existence has reflected a real renascence in general practice, and is a monument too to the wisdom and enthusiasm of those who have principally guided its destinies. The need for a permanent headquarters to house staff and provide a meeting-place is now pressing. The greater isolation from his colleagues that the family doctor in contrast to the consultant must perforce accept has made many members of the College acutely aware that the mitigation of this should be one of the College's chief aims. Specialized libraries of books, periodicals, and films to help the general practitioner will require space at the headquarters building, where there should be also meeting-rooms and a place for exhibitions. Moreover, as every professional man knows, merely to meet and exchange views in pleasant surroundings is not only refreshing but passes the acid test of increasing efficiency.

If bricks and mortar are expensive in London, education and research run away with the money anywhere. But these latter are essential to the College as it has, rightly, been conceived. Largely as a result of the College's work over the last few years, with invaluable assistance from Dr. W. P. D. Logan and the Registrar-General's staff, data have been gathered systematically on the large amount of morbidity that only general practitioners are in a position to investigate. The organizing of this kind of research is still in its infancy, and the College has an important role here. £1m. is a large sum, but the College has shown itself worthy of such a claim on the generosity of the community, both medical and lay. We would commend this appeal to the medical profession. Details of how to make donations may be obtained from the College of General Practitioners, 41, Cadogan Gardens, Sloane Square, London, S.W.3.

ROYAL COMMISSION'S REPORT

The Council of the B.M.A. was informed on Tuesday that the Minister of Health and the Secretary of State for Scotland had suggested a meeting "quite soon" with one or two representatives of the profession to "exchange views" on the Royal Commission's report. In a letter to the Secretary of the Association, who is also Secretary of the Joint Consultants Committee, the Minister of Health wrote, "We could then have a preliminary general discussion, and consider how subsequent negotiations could best be conducted." The Council welcomed the invitation of the Minister and appointed its chairman, Dr. S. Wand, to represent the B.M.A. at this preliminary general discussion. The Joint Consultants Committee had already asked its chairman, Mr. T. Holmes Sellors, to act for it in any exploratory meeting. A letter on this subject, which has been sent to Branches and Divisions by the Secretary of the Association, is published in this week's *Supplement* (p. 105).

Drug Treatment of Disease

PHARMACOLOGY OF HYPOTENSIVE DRUGS

BY

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The hypotensive drugs most widely used in current practice fall into five groups according to the site and mode of their main pharmacological actions—namely, the veratrum alkaloids, hydrallazine, the rauwolfia alkaloids, adrenergic blocking drugs, and ganglion-blocking agents. These groups will now be discussed separately. The most suitable regime of treatment for a particular patient, however, may well be a combination of drugs from two or more different groups, and, in addition, chlorothiazide has been shown to have a powerful potentiating effect on certain other hypotensive agents.

Veratrum Alkaloids

These substances are of some historical interest, since preparations of veratrum were used a century ago in the treatment of eclampsia. Many different alkaloids (e.g., protoveratrine, veratridine) and alkaloidal mixtures (e.g., "veriloid") are available, but the effects of each are broadly similar in the sort of doses used clinically. The drugs may be given intravenously if a rapid effect on the blood-pressure is desired, but are more usually given orally, by which route they are reasonably well absorbed.

The veratrum alkaloids act by eliciting the Bezold reflex. The sensory receptors for this reflex lie in the myocardium, and the afferent pathway is by way of the vagus nerves to the brain-stem; its effects include hypotension and slowing of the pulse, and there is also at the same time peripheral vasodilatation. Some experimental evidence exists for a direct action of the drugs on the central nervous system, but it is not certain how far this may play a part in man. Postural cardiovascular reflexes are not blocked by veratrum alkaloids, and postural hypotension is not a feature of their use.

The principal drawback to the clinical effectiveness of the veratrum alkaloids is their tendency to cause nausea and vomiting. The emetic dose is very close to the hypotensive dose, and this relationship holds for all preparations so far tested. Other unpleasant effects in some cases include paraesthesiae in the lips, tongue, and extremities, a feeling of constriction in the throat, or an epigastric or substernal burning sensation. These side-effects may be more prominent after oral administration than when the drugs are given intravenously. They appear to be less severe in patients with toxaemia of pregnancy, who often tolerate veratrum alkaloids well.

Hydrallazine

The chief interest in hydrallazine (1-hydrazinophthalazine) has centred round the ability of this drug under certain circumstances to increase the amount of blood flowing through the kidney at the same time as lowering the blood-pressure. This contrasts with the effect of other hypotensive agents, most of which, and particularly the ganglion-blocking drugs, tend to produce a diminution in renal blood-flow, especially in those patients in whom renal vascular narrowing is already severe.

The mode of action of hydrallazine is complex: it probably acts mainly on centres in the brain stem, but there is also evidence for a direct action on the peripheral vessels as well as a sympatholytic effect. The reduction in blood-pressure after hydrallazine tends to affect the diastolic proportionately more than the systolic pressure. The drug produces a tachycardia, which may be considerable, and an increase in output of the heart. Vasodilatation occurs both in viscera and in the extremities, and an increased blood-flow to the internal organs reflects the raised cardiac output. These effects are particularly seen after intravenous injection of the drug. Hydrallazine is also effective when given orally; with repeated administration by this route some tolerance occurs, and increasing doses may be necessary to maintain a hypotensive action.

Though there is no doubt that hydrallazine is capable of reducing the blood-pressure, its use as a single therapeutic agent is severely limited by the frequency of unpleasant side-effects which occur when an effective hypotensive dose is given. The commonest of these are headache, nausea and vomiting, palpitation, nasal stuffiness, and flushing of the skin. Anginal pain may be precipitated in subjects with coronary artery disease. A febrile reaction with rash may occur, and sometimes after prolonged administration a syndrome develops which has features in common with rheumatoid arthritis or disseminated lupus erythematosus and in which L.E. cells may be found in the blood.

Rauwolfia Alkaloids

Reserpine may be taken as an example of the group of rauwolfia alkaloids, since the actions of individual alkaloids and mixtures in this group are similar, and the majority of pharmacological studies have been carried out with this compound. The tranquillizing effect of reserpine is well-known, and this alone by relieving stress and anxiety may help to lower the blood pressure, but the drug also has a mild but definite hypotensive action in its own right, which becomes evident if the dose given is sufficiently large.

The main site of action of reserpine is a central one, probably on centres in the region of the hypothalamus. A feature of the drug is the long latent period before the onset of its action—namely, one hour or more even after an intravenous dose. The effect is prolonged and also wears off slowly. The drug's exact mode of action is uncertain; it is known to have the property of depleting tissues of 5-hydroxytryptamine (brain, platelets, intestine) and of noradrenaline (artery walls,

brain, adrenal medulla), though the relationship of this effect to its hypotensive action is not clear.

The reduction in blood-pressure which follows reserpine is accompanied by a bradycardia. Apart from this action, and its tranquillizing properties, the drug has many other pharmacological effects which may be of importance in individual cases. Intestinal motility is increased, which may lead to diarrhoea, though this effect may be useful in combating the constipation produced by ganglion-blocking drugs. Flushing of the skin, nasal congestion, and headache are not uncommon. There is an increase in the acidity of gastric secretion. More serious are the effects on the central nervous system which may be seen with larger doses of reserpine; these include mental depression, severe enough on occasion to lead to suicide, and a Parkinsonian syndrome of muscular rigidity and tremor. Other effects which occur in occasional cases are oedema due to sodium retention, and sometimes gynaecomastia and even lactation.

Reserpine potentiates the action of other hypotensive agents, particularly the ganglion-blocking drugs. Its most useful place in the treatment of hypertension would appear to be as part of a combined regime, in which only small doses of reserpine are given and the risk of serious side-effects is minimized.

Adrenergic Blocking Drugs

Of this group of drugs perhaps phenoxybenzamine has received most attention as a hypotensive agent. Phenoxybenzamine belongs to a series of compounds, the β-haloalkylamines, which are effective in blocking stimulation of the sympathetic nerves, but are even more active in blocking the effects of circulating adrenaline and noradrenaline. For this reason it may be used as a diagnostic or therapeutic agent in patients with phaeochromocytoma, though the shorter-acting phentolamine is usually preferred for this purpose.

Phenoxybenzamine may be given intravenously, and is also active when administered by mouth. Its chief pharmacological effect is to cause peripheral vasodilatation, well marked in the skin, which has led to the use of the drug in peripheral vascular disease. In sufficient doses it may also cause some reduction in blood-pressure, particularly in the erect position, since the normal postural vasomotor reflexes are blocked. This effect, however, is inconstant, and phenoxybenzamine has proved disappointing as a hypotensive agent, at any rate when used singly. It is possible that there may be a place for the drug in combination with other, more effective hypotensive drugs, but this suggestion awaits proof.

The recently introduced compound bretylium may also be mentioned under this head. This drug has an unusual action, in that it selectively blocks the peripheral sympathetic nervous system, apparently by accumulating on the adrenergic nerves, without inhibiting the effects of circulating or injected noradrenaline or adrenaline. Indeed, after administration of bretylium, injected noradrenaline has a greater pressor effect than before. It is too early to assess this drug fully, but it is clear that bretylium is effective in reducing the blood-pressure in many hypertensive patients, postural hypotension being particularly marked with its use. Side-effects reported are few, mainly excessive dizziness on standing and nasal stuffiness. A possible disadvantage is that the oral dose is several times greater than the effective parenteral dose, and absorption of the drug from the alimentary tract may be irregular.

Ganglion-blocking Drugs

The ganglion-blocking drugs include the most powerful and rapidly acting hypotensive agents known, and for this reason form the cornerstone of therapy in severe hypertension. They fall chemically and pharmacologically into two groups, the quaternary ammonium compounds, which are poorly absorbed from the gastro-intestinal tract and confined to the extracellular fluids of the body, and the freely absorbed and diffusible secondary and tertiary amines.

Quaternary Ammonium Compounds

The simplest of these, tetraethylammonium, has been known for many years, but as this compound has to be given by injection, and as its duration of action is only a matter of minutes, it is of little value in therapeutic practice. The discovery of pentamethonium and hexamethonium introduced for the first time ganglion-blocking agents with a duration of action long enough to be useful in treatment, and these drugs may be regarded as the prototypes of a long series of quaternary compounds which have been developed subsequently.

All these compounds are poorly absorbed, to the extent of only 5 to 10% of the dose, from the alimentary tract. Absorption is also irregular, depending on the relation of the dose to meals and the presence or absence of constipation, and for this reason these drugs are more safely given by injection. Those compounds which were developed later, such as pentolinium and chlorisondamine, appear to be absorbed somewhat more regularly when given by mouth than hexamethonium, but the oral dose is still considerably larger than the parenteral dose, and the possibility of irregular and excessive absorption is always present. An advantage of the latter drugs is that they have a slightly longer duration of action than hexamethonium, allowing less frequent dosage. All the compounds in this group are excreted entirely in the urine, so that they should be used with caution and in low dosage in the presence of renal failure.

The reduction in blood-pressure produced by the ganglion-blocking agents is most marked in the erect position, due to the blocking of postural vascular reflexes and pooling of blood in the lower parts of the body. This effect is increased when there is vasodilatation, such as after a meal, in hot weather, or when the patient is feverish; it is also augmented by sodium depletion or reduction in blood volume, or following sympathectomy.

All ganglion-blocking drugs so far tested clinically block the ganglia of the sympathetic and parasympathetic systems impartially. The many side-effects due to unwanted blockade of autonomic ganglia are familiar: constipation and abdominal distension are perhaps the most troublesome, but diarrhoea may also occur; blurring of near vision due to paralysis of accommodation, dryness of the mouth, difficulty in micturition, and impotence are all frequently seen. Toxic effects other than those due to ganglionic blockade have not been reported with the quaternary compounds.

Secondary and Tertiary Amines

With the discovery of mecamylamine, a non-quaternary ganglion-blocking agent was made available for the first time. This compound is a secondary amine, and the more recently introduced pempidine, which has many similarities, is a tertiary amine. Both mecamylamine and pempidine have the great advantage that they are fully and regularly absorbed when given by mouth and are therefore more convenient to use in clinical practice. Both drugs are largely excreted in the urine, and their rate of excretion is influenced by urinary *p*H, being greater in an acid and less in an alkaline urine. The chief disadvantage of mecamylamine is that it is very long-acting, so that the dose can only be built up gradually, and if untoward side-effects occur they tend to be prolonged as the drug is slowly excreted. Pempidine is excreted more rapidly, and this makes for easier control of dosage; correspondingly its shorter duration of action (5–6 hours after an oral dose) means that pempidine needs to be administered at more frequent intervals than mecamylamine.

Mecamylamine and pempidine are freely diffusible across cell membranes, and in fact are more concentrated inside the cell than outside the plasma or extracellular fluid. Their exact mode of action is likely to be different from that of the quaternary ganglion-blocking compounds, but their effect is similar, and symptoms from parasympathetic blockade are equally, if not more, frequent with these two drugs. In addition, mecamylamine may sometimes produce alarming symptoms of toxicity to the central nervous system—tremor, confusion, and delirium—though usually only when given in large doses and in the presence of some degree of renal failure.

Chlorothiazide

This drug, in addition to its diuretic action, has a powerful potentiating effect in the hypotensive action of various drugs, in particular the ganglion-blocking agents. In the case of the quaternary ganglion-blocking compounds (such as hexamethonium and pentolinium), this effect of chlorothiazide appears to be principally related to the reduction in volume of the plasma which accompanies the sodium depletion produced by the drug, since the increased sensitivity to the ganglion-blocking agents may be abolished by restoration of the lost plasma volume with sodium-free dextran. It is likely that this also applies to the potentiation by chlorothiazide of the secondary and tertiary amines mecamylamine and pempidine, though the different chemical behaviour of these latter compounds suggests the possibility that other additional factors may play a part.

Chlorothiazide has no direct hypotensive action *per se*, and intravenous administration of the drug is without effect on the blood-pressure. After repeated dosage, however, some hypertensive subjects may develop postural hypotension, and this is particularly noticeable in patients who have undergone sympathectomy. This effect also appears to result from the diminution in plasma volume brought about by chlorothiazide.

Conclusion

There is thus available a wide range of hypotensive agents, many of them active at different points in the circle of reflexes which helps to maintain the established state of hypertension. With our present knowledge, the most satisfactory therapeutic effect in a particular case can be obtained by trial and error, using drugs from the several different groups, either singly or more often in combination.

SHOES FOR CHILDREN

A SURVEY OF RETAIL SHOE-SHOPS IN THE BOROUGH OF EALING

BY

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Doctors and health workers can readily describe suitable designs of children's shoes which promote the growth of healthy feet, but are these shoes in fact to be obtained in the shops? Parents tell of the difficulty experienced in finding shoes of correct style and size, but how true is this? and to what extent can the blame be with the manufacturers for not making such shoes, or with the retailers for not stocking them? If the retailers have them, do they stock a sufficient range of sizes and fittings? How often do the retailers stock other girls' shoes of inferior design as, for example, the fashionable casual style? Again, if well-designed shoes are stocked in the shoe-shops, is it the fitting by the assistants that is at fault? Can it be that the poorly designed shoes are cheaper than the well-fitting ones?

To try to find the answer to some of these questions, an inquiry, by means of a questionary, was made in the Borough of Ealing during the period January–June, 1958. Ealing has long been concerned about the damage done to children's feet by ill-fitting shoes, and has produced much valuable and original research in the past 10 years. Surveys carried out by Dr. D. A. Craigmile in Ealing revealed the incidence and variety of foot defects in children, many of which are known to cause foot pain in adults. The Ealing Contributory Shoe Scheme clearly showed that many of these acquired foot defects can be cured or improved by well-fitting shoes alone. At the present time in this area a foot health nurse visits the schools, inspects the children's feet, and records her findings. Children with early foot defects and in need of advice are asked to attend the foot clinics at which the particular problem can be discussed with the parents. Ealing can thus be regarded as having a high standard of foot care.

In this inquiry the visits to the shoe-shops were carried out by the foot health nurse and myself only, in order to keep the personal error as small as possible. The questionary was completed in each case by one of us in the shop at the time of the interview with the manager, who was on the whole most interested and helpful. Occasionally the manager thought he should first seek permission to answer the questions from his employer, in which case the questionary was left with him for completion and was subsequently collected or returned by post.

A list of footwear retailers in the Ealing area was obtained from the Public Health Inspectors Department. Out of 49 shops selling shoes, 39 sold children's shoes. Of these 39 shops 3 were multiple stores—for example, Woolworths. Some of these 39 shops were branch shops

of one particular firm, but as their stocks of shoes were found to differ with the individual manager's choice, they were counted as separate shops in this survey.

In two shops the managers were unwilling to co-operate. In 15 shops the questionary had to be left with the manager concerned; of these, four were never recovered though a letter of reminder was sent, and in eight cases the questionary was incomplete or inaccurate. These were discarded and the final analysis was made with the results from 25 shops.

At the time of the questionary (mid-year, 1958) the population of Ealing was 183,000, and the number of children aged 1–15 years was estimated at 34,000.

Description of Questionary

The questionary was devised in the form of a series of questions, followed by the possible answers, of which the pertinent answer was ringed by the questioner in each case. For example: (1) Do you stock shoes with rounded toes and straight inner borders? . . . Yes./No. (2) Are all or some or none of your assistants trained to fit children's shoes?

The questionary was in seven main parts.

Part I.—This ascertained whether suitable children's shoes were stocked and, if so, whether they were in half-sizes and width-fittings. How many width-fittings? Were these shoes of a lace-up style or bar-instep style,* or both? Were they stocked for toddler aged 1–3 years, infant aged 3–7 years, junior aged 7–11 years, and senior aged 11–18 years? Were these shoes stocked in large sizes—that is, size 7, 8, 9, and 10 for boys and girls?

Part II.—Besides these well-shaped shoes, what other styles for girls were stocked in the shop? That is, did the shop stock (1) double ankle-bar, (2) high-cut casual, (3) low-cut casual shoes?

Part III.—Did the shop recommend or sell only one make of shoe, or several?

Part IV.—Did the shop carry a stock of the good shoes with (*a*) half-sizes and (*b*) width fittings in all, or some, or none of the shoes? The manager was then asked to show a narrow-fitting shoe (10c child's shoe) and a large-size shoe (8 girl's shoe) as a check of the shop's stock at the time of the survey. Could the shop obtain shoes out of stock in one day, two or three days, one week, or several weeks? Did they try to do this?

Part V.—Four shoes were specified and the prices asked. For example, a request was, "Quote the price of size 5 toddler's shoe in brown leather and composition sole."

Part VI.—In this shop do all or some or none of the assistants fit children's shoes during busy periods? By whom are the assistants trained? Do they attend a refresher course of training once, or periodically, or never?

Part VII.—Did the shop employ an *x*-ray machine for fitting; if so, did they rely on it a great deal or a small amount when fitting children's shoes.

Results

Part I.—Table I shows the results of Part I of the questionary. All 25 shops stocked a well-shaped shoe—that is, with rounded toe and straight inner border. Of these, 17 shops had half-sizes in all these shoes and five had half-sizes in some of them. Fifteen shops stocked width-fittings in all these shoes; two stocked width-fittings in only some of these shoes. Yet of the 17 shops with these shoes in width-fittings, only four stocked four width-fittings, seven stocked three width-fittings, and six stocked two width-fittings. A lace-up style of shoe was common to all 25 shops, but 19 also stocked a bar-instep style. These well-shaped shoes were well stocked for infant age range (3–7 years) and junior age range (7–11 years), but less so for toddler age range (1–3 years), and only 14 shops had these shoes for age range 11–18 years. The range of large sizes in these shoes was very poor, particularly for girls.

Parts II and III.—Table II shows how many shops stocked other inferior designs of girls' shoes. All 25 stocked a high-cut casual style and 17 shops stocked the low-cut casual style. Eight shops stocked one make of shoe. Yet of these eight shops only four carried an adequate range of half-sizes and three width-fittings.

Part IV.—Table III shows the extent of the stock of well-made shoes in the 25 shops. Only six shops stocked half-sizes in all their well-shaped shoes, and 15 shops stocked half-sizes in some of these shoes. Five shops had three width-fittings or more in all their stock of well-shaped shoes. Twelve shops had width-fittings in some of the well-shaped shoes, but only five of these stocked three or more width-fittings. On asking to see two selected shoes as a check on the stock of the shop at the time of the visit, only 12 shops could show a narrow-fitting child's shoe, size 10c, and only eight could show a large-size girl's shoe, size 8. Nineteen shops took one week to obtain shoes out of stock; three shops took only two or three days. Twenty-two shops tried to obtain shoes out of stock for their customers.

Part V.—Four children's shoes were described to obtain the price. The results showed two basic price

TABLE I.—*Details of Well-shaped Shoes in 25 Shops*

		No. of Shops
Good shoe stocked		25
Half-sizes	All	17
	Some	5
Width-fittings	All	15
	Some	2
No. of width-fittings	4	4
	3	7
	2	6
Lace-up style		25
Bar-instep style		19
Age	1–3 years	15
	3–7 ,,	21
	7–11 ,,	23
	11–18 ,,	14

Large Sizes		B	G
Boys	Girls		
7	7	14	11
8	8	8	7
9	9	5	0
10	10	2	0

TABLE II.—*Details of Badly Designed Girls' Shoes in 25 Shops*

	No. of Shops
Double ankle-bar	7
High-cut casual	25
Low-cut casual	17
One make stocked	8

TABLE III.—*Number of Shops Having a Comprehensive Stock of Half-sizes and Width Fittings, and Time Taken to Obtain Shoes Out of Stock*

		No. of Shops
Half-sizes in	All	6
	Some	15
	None	4
Width-fittings in	All	5
	Some	12
	None	8
Able to show	10C shoe	12
	Girls 8	8
Time to obtain shoes out of stock	2–3 days	3
	1 week	19
	2–3 weeks	2
No. which did this		22

*Bar-instep style denotes a shoe with a strap across the instep.

ranges. The more expensive range was that in which the shoes had width-fittings. In the cheaper range the shoes had no width-fittings. These results are analysed in Table IV.

TABLE IV.—*Details of Price Range of Four Specified Shoes According to Whether Width-fittings were Stocked*

	Shops with Width-fittings	Shops with No Width-fittings
Size 5 toddlers	14s. 6d.–21s. 9d.	8s. 0d.–15s. 11d.
12½ brown leather, composition sole	24s. 11d.–37s. 6d.	21s. 9d.–26s. 9d.
12½ brown leather, leather sole ..	26s. 11d.–43s. 6d.	21s. 9d.–27s. 11d.
7 boys' brown leather, crepe rubber sole	31s. 11d.–55s. 0d.	26s. 9d.–39s. 6d.

Part VI.—Table V shows that out of the 25 shops, 14 allowed all their assistants to fit children's shoes; eight allowed only some of their assistants to do so, and one shop had one assistant only who did the fitting of children's shoes; 16 shops trained all their assistants to fit children's shoes, and six trained some of them. Eight shops allowed untrained assistants to fit children's shoes at busy periods. The training in 16 shops was

TABLE V.—*Details of the Fittings of Children's Shoes in 25 Shops*

		No. of Shops
Fitting by assistants	All	14
	Some	8
	None	1
Whether trained	All	16
	Some	6
Untrained assistants fitting in busy periods	..	8
Training by	Manager	16
	Firm	4
	Course	0
Refresher course	Periodically	11
	Once	1
	Never	9
X-ray machine used	.. ..	8
Value of machine	Great	0
	Little	8

done by the manager and by a firm in four shops. None of the 25 shops sent their assistants to a shoe-fitting training course. Eleven shops gave their assistants refresher courses in shoe-fitting from time to time, but nine never did.

Part VII.—Eight shops used an *x*-ray machine for fitting, but they all agreed it was of little value.

Discussion

Though there are many criteria that can be used to define a well-designed shoe, only two were used in this survey. A suitable children's shoe was defined as having a rounded toe and a straight inner border. All the 25 shoe-shops stocked such a shoe.

Other surveys have shown that to fit a high proportion of children's feet there must be at least three width-fittings to every half-size (Craigmile, 1953). The Somerset survey, carried out with the co-operation of Clarks shoe firm, stated that with their multi-fitting range of shoes, 92% of girls and 87% of boys could be properly fitted in winter, and 98% of girls and 95% of boys with summer sandals (County Medical Officer, Somerset, 1953). The Satra House Research Report (RR98), "Dimensions of Children's Feet," showed that a range of five width-fittings would cover 95% of children's feet and three width-fittings 91% of children's feet. This Ealing survey shows how poor is the stock of width-fittings in the shoe-shops, for less than half of them stocked three or more width-fittings.

Though well-designed shoes were found to be adequately stocked for the age-group 3–11 years, fewer shops catered for the 11–18 age-group. This infers that men's and ladies' styled shoes are usually sold to this age-group.

A very poor stock of shoes of the larger sizes was found in the shops. This obviously adds a further difficulty to the parents of children with big feet, and, in the case of girls, encourages the purchase of a ladies' style shoe.

Inferior Styles of Girls' Shoes.—A girl's shoe is made to look "pretty" or "fashionable" by altering the basic details of a well-designed shoe in one of the following ways:

(*a*) The site of the strap in a bar-instep style is changed from the side of the shoe to the back, doubled, and fastened by a button across the front of the instep. The toe shape remains unchanged, but because of the inadequate grip of the double strap at the instep the shoe fits poorly. Luckily, this double-ankle-bar style is a dying fashion, but it can still be found in the toddler age-group. Seven shops stocked this style.

(*b*) The toe shoe is altered by curving the inner border of the shoe inwards to meet the outer border at a point of varying degree. The straight inner border and generous rounded toe shape are thus lost. The upper of the shoe is made to fit tightly across the metatarsal arch of the foot, and this, plus the "digital wedge" effect described by Haines and McDougall (1954), keeps the shoe applied to the foot. This design of shoe is much in favour with parents of older girls and with the shoe-fitters. Twenty-five shops stocked this style of shoe.

(*c*) It is surely true to say that the low-cut casual style of shoe has no residual good features of design at all. These shoes have pointed toes, low-cut sides, and low-cut fronts. They stay on the foot because they are "short-fitted" in length, narrow in width, and use the toes as a "digital wedge." Seventeen shops stocked such a shoe. The results of this survey show how often the shoe-shops cater for the fashion-conscious girl by stocking these casual shoes. These sell well, and can be shown to parents when the shop itself has not got the correct fitting in a well-shaped shoe, or when the parents want a more grown-up style, or when the girl is allowed to choose her own shoes.

Eight shops stocked and recommended one make of shoe. Yet of these only four had the adequate range of half-sizes and three width-fittings to cover accurate fitting of children's feet.

Size of Stock.—The results as expressed in Table III show how poor was the extent of the stock of well-shaped shoes. Only 12 shops could show a narrow-fitting child's shoe, and only eight could show a large size for girls. The present custom of selling children's and adult shoes together from any one shop limits the size of the stock. The retailers claim that in order to stock a comprehensive range of half-sizes and three width-fittings in children's shoes, their shops would have to be enormous. There is an obvious need for the establishment of shoe-shops in which only children's shoes will be sold and where a sufficient range of sizes and width-fittings can be stocked. However, even with the existing system of selling children's shoes, the size of the stock would be relatively unimportant if the time taken to obtain shoes not in stock was one or two days. This survey shows, however, that the usual time to obtain these shoes is one week, which is far too long an interval. Shoes out of stock could be obtained in 48 hours if the manufacturers were contacted immediately.

Price Range of Four Specified Shoes.—The prices quoted by the managers had, of course, a wide range, but on analysis were found to fall into two groups. The more expensive were those of shoes with width-fittings, but the two price-ranges show an overlap, clearly demonstrating that all shoes for children could be multi-fitting and yet reasonably priced.

Fitting of Children's Shoes.—The fitting of any shoe is a skill requiring training and experience, and particularly is this true with children's shoes. Many firms have their own foot-gauges, which are very useful, but in addition a trained assistant should be able to fit by hand.

Table V shows that the training of shop assistants is not nearly good enough. Much selling of children's shoes takes place unfortunately on a Saturday, when the shops are very busy; some shops employ young unskilled girls on that day as a source of extra help. In fact, eight managers admitted that they allow untrained assistants to fit children's shoes in busy periods.

The training of assistants was found to be usually done by the managers themselves. Only four shops used training by a shoe firm, and none of the 25 shops sent their assistants to a training course in shoe-fitting. Less than half the shops allowed their assistants to attend a refresher course.

Only a third of the shops used *x*-ray machines, and all agreed that these machines were of little use in the fitting of children's shoes.

Summary

A survey of 25 shops selling children's shoes is described. All the shops were found to stock well-designed shoes for children. Very few shops, however, stocked a comprehensive range of half-sizes and three width-fittings in these shoes, and such a range is essential to fit the majority of children's feet. Only half the shops kept these shoes for children of 11–18 years. Stocks of larger shoes, of size 7 and over, were also limited.

Yet all 25 shops stocked the inferior-styled girls' shoe known as the "casual."

There was an unnecessary time-lag in obtaining shoes out of stock. Adequate training of shop assistants in the art of fitting children's shoes was lacking. The few shops that employed an *x*-ray machine found it of little value in shoe-fitting.

It was shown that all well-designed children's shoes could be multi-fitting and yet be reasonably priced.

The need to establish shops which sell only children's shoes is discussed.

I am indebted to Mrs. B. Murton, S.R.N., foot health nurse, for her help with the survey, and to Dr. W. G. Booth, joint area medical officer, Middlesex County Council Area No. 7, Ealing, for his encouragement and advice.

While permission for publication has been given, Middlesex County Council take no responsibility for the opinions expressed therein.

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INVESTIGATION OF VISUAL ACUITY OF DRIVERS

BY

D. J. K. WILKIE, M.R.C.S., D.O.M.S.
Sheffield

This investigation was carried out in routine ophthalmic practice. Out of a total number of 4,422 patients, 1,011 were holders of current driving licences.

Ministry of Transport and Civil Aviation Regulations Governing Eyesight of Motor Drivers

The diseases and physical disabilities which are a bar to the granting of a driving licence are prescribed in the Motor Vehicles (Driving Licences) Regulations, 1950 (S.I. 1950. No. 333), and include: "Inability to read at a distance of 25 yards in good daylight (with the aid of glasses if worn) a series of six letters and figures in white on a black ground of the same size and arrangement as those prescribed for the identification mark of a motor-car."

The analysis of the visual acuity of these 1,011 patients is:

460 (45.5%) able to read a number-plate at 25 yards without the aid of glasses.
476 (47.1%) in possession of distance glasses and, with their aid, able to read a number-plate at 25 yards.
75 (7.5%) not in possession of distance glasses, not able to read a number plate at 25 yards.

The analysis of the age groups of the 75 patients with vision below the required standard is: 16–20, 4%; 21–30, 8%; 31–40, 8%; 41–50, 36%; 51–60, 22%; 61–70, 12%; over 70, 10%.

Fifty-two (69.3%) of these patients were unaware, or professed to be unaware, of the fact that their distance vision was defective. It will be noted that inadequate distance vision is the greatest in age-groups 41–60 (58%). This can be accounted for by the fact that most of them have only moderate errors of refraction for which previously, when they were younger, they had been able to compensate, and deterioration of vision was so gradual as to be unnoticeable.

There were four in those aged 61 to over 70, whose vision could not be improved with glasses. This was due to senile macular degeneration in two cases and two had immature cataracts. There was also one person aged 52, with congenital nystagmus, whose vision had obviously never been up to the required standard, and one aged 39 with optic atrophy. All these patients were advised to cease driving at once. Four agreed and two flatly refused.

Five of the cases seen had failed their driving test owing to alleged defective vision. Two of these were found to have normal vision; the other three required glasses. From this it is apparent that sometimes the examination of vision carried out on the occasion of a driving test is inadequate. Standard conditions are presumably, at these times, not available—for example, the number plate used may be dirty, the distance may not be correct, and the lighting conditions may be poor.

Ability to Read a Number Plate at 25 Yards.—It is suggested that the onus of proof in this matter should no longer rest with the applicant, but with the licensing authority. The reasons for this are: (1) the severe and

increasing accident rate; and (2) because a large number of drivers appear to be unaware of the fact that they are unable to see a number-plate at 25 yards—for example, according to Ministry of Transport regulations.

Suggested Scheme

All licensing authorities should set aside a room for a simple sight test, and applicants who choose can have their vision checked (with glasses, if worn). If the vision is found to be deficient, they should be given a small form which can be taken to an ophthalmic surgeon, their own doctor, or a sight-testing optician, and a licence should not be issued until this form is filled in to the effect that the vision has been improved to the required standard with glasses.

Applicants who do not wish to attend at the licensing department should be supplied with the above form, which can then be filled in, in the same manner.

If it has been proved that the applicant requires glasses for driving, then his driving licence should be stamped "With glasses."

A small, inexpensive sight-testing apparatus, as foolproof as possible, has been devised, which could be supplied to all licensing authorities, ophthalmic surgeons, general practitioners, and sight-testing opticians. It consists of an illuminated facsimile of a number-plate (six different sets of plates available for each apparatus). The type can be used at 6 metres, or, with reversed lettering and a mirror, at 3 metres (see Diagram).

I am indebted to Theodore Hamblin Ltd. for their help and advice in the designing of the apparatus.

COLLEGE OF G.P.s' APPEAL

The following is the first list, issued by the College of General Practitioners, of individuals and organizations who have contributed to the £1m. appeal launched by the College (see also p. 716). Members of the College have subscribed about £10,000.

John Wyeth and Brother Ltd., £500; two anonymous donors, £1,000; Glaxo Charity Trust, £35,000; Allen and Hanburys, £14,000; Lord Woolton, £1,632; Paines and Byrne Ltd., £525; Beecham Group Ltd., £35,000; Crookes Laboratories Ltd., £50; Boots Pure Drug Co. Ltd., £10,000; Cyanamid of Great Britain Ltd., £7,000; James Capel and Co. Ltd., £15; Mrs. Christopher Soames, £1 1s.; G. D. Searle and Co. Ltd., £5,714; Wellcome Foundation, £35,000; Fisons Ltd., £7,000; Mrs. Mary Wilkinson, £5; Albright and Wilson Ltd., £700; Sir Harry Jephcott, £1,142; Pfizer Ltd., £14,000; Laporte Industries Ltd., £26; Lord Leathers, £100; Baring Bros. Ltd., £500; British Drug Houses Ltd., £2,100; Thomas Kerfoot and Co. Ltd., £105; Bowater Paper Corporation Ltd., £1,050; Kaylene (Chemicals) Ltd., £52; Lazard Bros. Ltd., £500; Smith Kline and French Labs. Ltd., £14,000; Eva Lady Buxton, £10; May and Baker Ltd., £14,000; M. G. A.

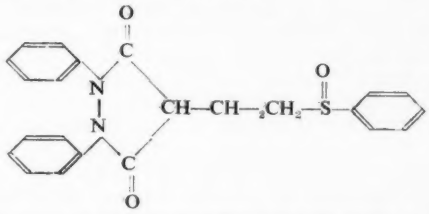
(*Continued at foot of next column*)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

"Anturan" (formerly G28 315) (Geigy).

Chemistry.—Anturan is a derivative of phenylbutazone and is 1,2-diphenyl-3,5-dioxo-4-(2′-phenyl-sulphinylethyl)-pyrazolidine. Structural formula:



Pharmacology.—Anturan differs from the parent substance phenylbutazone in having a much stronger uricosuric effect and much weaker analgesic and anti-inflammatory effects. The uricosuric action is effected by blocking the reabsorption of urates by the renal tubules. In this way the excretion of urates may be increased by up to 700%. Its action is opposed by the simultaneous administration of salicylates or citrates. The effect of the drug on electrolyte balance is trivial and much less than that of phenylbutazone.

Therapy.—Anturan is the most potent uricosuric agent available for the therapy of gout. Its effect is limited to enhancing excretion of urates; it has no direct effect on acute gout, for which phenylbutazone and colchicine remain the drugs of choice. The long-term effect of maintaining blood levels of uric acid at or near normal in gouty subjects reduces the frequency and severity of acute attacks, and tophi have been seen to diminish. Hyperuricaemia may, in addition, be harmful to kidneys and blood vessels. So far as is known, administration of anturan would have to be continued indefinitely, the dose being controlled by periodical estimations of uric acid in the serum.

Toxic Effects.—These are reported as being slight and limited to gastro-intestinal disturbances, but, as with all pyrazoles, blood dyscrasias should be watched for. Renal colic due to precipitation of urate in the renal tract can be avoided by giving adequate fluid, and by maintaining the urine alkaline with potassium acetate or sodium bicarbonate (not with citrate). Acute attacks may, as with other uricosuric agents, be precipitated during the early stages of treatment. The drug should therefore be given in small doses (200 mg. a day at first), the dose being gradually increased up to 800 mg. a day, depending on the clinical response and the level of uric acid in the blood.

Contraindications.—Patients known to be intolerant to phenylbutazone should be carefully observed. The presence of a peptic ulcer is a contraindication. Renal failure is not of itself a contraindication, though the effect on renal function will require study in each case.

N.H.S. Basic Price.—100 100-mg. tabs., 46s. 8d.

(*Continued from preceding column*)

Watson, £5; Charterhouse Group Ltd., £10; N. M. Rothschild Ltd., £100; Australian Mercantile Land and Finance Co. Ltd., £25; Abbott Laboratories Ltd., £1,142; Messrs. Coutts and Co. Ltd., £100; Mrs. Singer, £1,000; Council Members, £3,362; Amplivox Ltd., £105; Allied Laboratories Ltd., £1,000; Westminster Bank Ltd., £250; Barclays Bank Ltd., £250; National Provincial Bank Ltd., £250; Royal Exchange Assurance Co. Ltd., £25; Marlin Management Co. Ltd., £210; A. Wander Ltd., £1,050; Mayfair Manufacturing Co. Ltd., £180; Martins Bank Ltd., £50; Midland Bank Ltd., £250; Lloyds Bank Ltd., £250; Roche Products Ltd., £7,000; Mr. Basil Samuel, £52; Hoare's Bank Ltd., £50; Arthur Cox and Co. Ltd., £2 2s.; Joseph Rank Ltd., £1,000; H. K. Lewis and Co. Ltd., £100.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Congenital Dislocation of the Hip

SIR,—Dr. R. A. Strang, in his letter (*Journal*, January 23, p. 279) raises the important subject of early diagnosis of congenital dislocation of the hip. Though there may be disagreement about the best method of treatment of this condition there can surely be no disagreement about this important aspect of the problem.

There are two difficulties to face in early diagnosis: (1) In this country the condition is uncommon. In this hospital we receive 15 children each year with C.D.H. from a population of 1,500,000 with approximately 700 doctors. It is very difficult to maintain enthusiasm for diagnosing a condition which may be seen only once in a practising lifetime of 40 years. (2) The hips are not commonly dislocated at birth. The dislocation does not take place suddenly but gradually over a period of days, weeks, or months. It results from the flexed hips of the foetus becoming the extended hips of the child. All normal children have flexion deformities of the hips at birth.

Most children in this country are born at home, where diagnosis is difficult, and Dr. Strang's suggestion of routine examination at welfare clinics is a good one. In this area we have tried to encourage routine examination of the hips when immunization inoculations are given at about four months of age. Most of the patients picked up at this age need only simple abduction of the hips for a few months, after which a good result can be expected.

There is, however, an extension of this problem. Congenital dislocation of the hip, even in this country, is not nearly as uncommon as is to be judged from the numbers diagnosed in infancy. Osteoarthritis of the hip is a common condition in later life. Wiberg[1] in Sweden and Lloyd Roberts[2] in this country, have stated that 20–30% of all cases of osteoarthritis of the hip are due to some degree of subluxation, but of course by the time a diagnosis is made it is called osteoarthritis. Had these subluxations been diagnosed in infancy a comparatively short period of protection of the hips in the abducted position would probably have prevented the subsequent osteoarthritis. The degree of subluxation in these hips may have been so slight that it would be difficult even with such excellent tests described by Ortolami[3] or with routine radiography (which would not be justifiable) to be certain of diagnosing them all.

It is not illogical to suggest that if all hips were protected during the dangerous first four months of life by being maintained in an abducted position (which also protects against extension) and never being allowed to adduct, not only would there be a reduction in the incidence of congenital dislocation of the hip immediately but also in the incidence of osteoarthritis in the more distant future.—We are, etc.,

E. W. SOMERVILLE.
J. C. SCOTT.

Nuffield Orthopaedic Centre,
Headington, Oxford.

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[1] Wiberg, G., *Acta chir. scand.*, 1939, **83**, Suppl. 58.
[2] Lloyd-Roberts, G. C., *J. Bone Jt Surg.*, 1955, **37B**, 8.
[3] Ortolami, M., *La Lussazione Congenita Dell'Anca*, 1948. Bologna.

SIR,—There is one very important fact to be appreciated from Dr. R. A. Strang's significant letter (*Journal*, January 23, p. 279). Clinicians who hope to make an early diagnosis of congenital dislocation of the hip should not be looking for an actual dislocation, but for signs of a puzzling condition not easy to diagnose with certainty, even with the use of radiography. That condition, commonly termed dysplasia, may lead to a gradual dislocating of the head of the femur from its socket. Even though there is evidence that dislocation is not an inevitable aftermath of dysplasia, it seems advisable to substitute the term congenital dysplasia of the hip for the term congenital dislocation. The word dislocation is misleading and to describe it as congenital is confusing.

Because there is debate concerning the most reliable signs of dysplasia, reserve and caution are imperative in making a firm diagnosis. To review such debate is beyond the scope of this short letter, but it must be clearly understood that the diagnosis of dysplasia cannot be made on just one examination. Furthermore, the opinion of an expert should always be sought. Lastly, if the expert confirms the diagnosis of dysplasia, but does not recommend immediate treatment, it is important for the parents to realize that the infant has still to be carefully examined at regular intervals before advanced crawling and early walking begin.—I am, etc.,

R. D. LAURENSON.

Anatomy Department,
Queen's University,
Kingston, Ontario.

Bleeding Oesophageal Varices

SIR,—By contrasting the discomfort to the patient and the high incidence of complications with the relatively low therapeutic benefit, Professor Sheila Sherlock and her associates (*Journal*, January 23, p. 227) are the latest to echo the disillusionment experienced by those who have used balloon compression routinely in the treatment of bleeding oesophageal varices.

Since adopting an alternative approach[1] based on the immediate use of neomycin and the withdrawal of protein as prophylaxis against coma, together with adequate blood transfusions and other measures to reduce the ill effects of haemorrhage, it has become evident that the need for intubation can be drastically reduced. Patients in whom exsanguination occurs (a smaller proportion than is traditionally supposed), or in whom coma develops despite treatment, still require the use of balloon compression. Intubation is justified despite its complications in this group, as the prognosis is very poor unless haemorrhage can be controlled, and as several patients can be rehabilitated once bleeding has ceased.—I am, etc.,

W. H. J. SUMMERSKILL.

Mayo Clinic,
Minnesota, U.S.A.

REFERENCE

[1] Summerskill, W. H. J., *Brit. med. J.*, 1958, **2**, 1322.

Diets for Lowering Serum Lipids

SIR,—With reference to the article by Dr. T. R. E. Pilkington *et al.* on "Practical Diets for Lowering Serum Lipids" in your issue of January 2 (p. 23), I am very surprised at the statement: "There have been few studies showing that a regimen containing unsaturated fats can be used by patients in their home surroundings and may be effective over long periods." The only references to this statement given are Groen *et al.*[1] and Malmros and Wygand.[2] I should like to draw attention particularly to the following communications on this

subject which seem to have escaped the attention of the authors: (1) "Studies on the Regulation of the Serum Cholesterol Level in Man"[3]; (2) "A Practical Dietary Regimen for Decreasing the Serum Cholesterol Level"[4]; (3) "Eat Well and Stay Well," by A. and M. Keys.[5] The contents of the first reference were communicated to the International Nutrition Congress at Paris in 1957 and were in the *Proceedings*. Both the first and second references were quoted in a Symposium by members of this department in the *Postgraduate Medical Journal*.[6] Other references under this general heading are quoted in *Nutrition Reviews*.[7]—I am, etc.,

Department of Medicine,
University of Capetown,
South Africa.

JOHN F. BROCK.

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[2] Malmros, H., and Wigand, G., *Lancet*, 1957, **2**, 1.
[3] Gordon, H., and Brock, J. F., *S. Afr. med. J.*, 1958, **32**, 397.
[4] —— ibid., 1958, **32**, 907.
[5] Keys, A., and Keys, M., *Eat Well and Stay Well*, 1959. Doubleday, New York.
[6] *Postgrad. med. J.*, 1959, **35**, 186 and 216.
[7] *Nutr. Rev.*, 1959, **17**, 291.

Pyloric Obstruction by Mucosal Diaphragm

SIR,—Mr. Digby Chamberlain and Mr. N. V. Addison (*Journal*, December 19, p. 1381) describe pyloric obstruction due to a mucosal diaphragm and they conclude that "the condition is of obscure origin, and no definite suggestion concerning its pathology can be made." The obscurity vanishes when it is realized that the mucosal diaphragm is none other than the pylorus, not the muscular one described by the anatomist, but the mucosal one seen by the radiologist. The reason why this iris-like diaphragm becomes obstructive appears clearly from the account of my own patients.[1]—I am, etc.,

Sydney, Australia. V. J. KINSELLA.

REFERENCE

[1] Kinsella, V. J., *Lancet*, 1951, **2**, 18.

Pathology for the G.P.

SIR,—In the *Journal* of February 6 (p. 415) Dr. D. Stark Murray described the clinical pathological services available for the G.P. There is one investigation which I am sure many G.P.s would value but which at present appears beyond the normal services provided by hospital pathological departments. I refer to the post-mortem examination. If a patient is admitted to hospital, the examination is easily arranged. Should the G.P. continue domiciliary care, however, he finds it, in my experience, impossible to get a P.M. done, unless he refers the case to the coroner.

In a recent case my patient died from an undiagnosed massive abdominal swelling, possibly a retroperitoneal sarcoma. Even though the hospital services may be willing to do the necropsy, I understand that the ambulance services are very unwilling to transport dead persons. Domiciliary pathological services could not be invoked. It was not a case for police transport. Having obtained the consent of the relatives, one can hardly ask them to pay for transport to and from hospital, let alone the possible cost of a necropsy. There must be many G.P.s who would welcome the opportunity to know a post-mortem diagnosis in puzzling cases. As far as I am aware, there is no service available to them under the N.H.S. in this contingency. Perhaps other areas have solved this problem.—I am, etc.,

Huddersfield. S. L. HENDERSON SMITH.

Guidance or Treatment

SIR,—Further correspondence on this topic prompts me to express my warm endorsement of your admirable leader on this subject (*Journal*, December 19, 1959, p. 1391). It would be unnecessary to comment further on the preamble to the Ministry of Education circular (347) were it not that it does represent the concepts that will influence the development of the child psychiatric services of the country. "The term 'child guidance' in the broadest sense is synonymous with education itself and is a process in which both parents and teachers are constantly engaged," has only to be translated into the field of physical health to reveal its limitations, viz., "the maintenance of physical health in the broadest sense is synonymous with education itself and is a process in which both parents and teachers are constantly engaged." Unimpeachable as are both statements, the latter conveys as little of the practice of medicine as does the former of the practice of child psychiatry.

Two undoubted truths confuse discussion on the topic of child psychiatric services. All children, however handicapped or ill, undoubtedly benefit from continued sympathetic interest and concern, which is available to them in child-guidance units and child psychiatric clinics and indeed in many other places. A capable child psychiatrist with an enlightened school medical officer can achieve a satisfactory service, however adverse the administrative set-up. Nevertheless, error or bias in the underlying ideas that govern the development of a wide-ranging service continually exercise an influence detrimental to the effectiveness of the whole service.

The Child Guidance Movement contributed largely to the effectiveness of child psychiatry 30 years ago by urging the importance of emotional elements in the child and in the environment, including educational influences. By a curious development the other elements implicit in child psychiatry were gradually dropped from the movement, which was originally comprehensive. Now, to create units widely, organized only to deal with emotional and educational elements, is to freeze a fluid state of development. To separate the psychiatric syndrome of childhood from those of adolescence and adult life and from the hospital situation in which they can be adequately investigated can now be regarded only as reactionary. This is not to argue that the local authority services and educational authorities must be excluded from the child psychiatric services to which they have contributed so largely. Every region and highly populated areas, however, should have a central child psychiatric clinic wholly staffed by and within the hospital service, and situated in relation to a psychiatric or paediatric hospital. Based on this central clinic joint services could then be established with the local authorities in the surrounding area. Such development should go hand in hand with the development of in-patient units in relation to the central hospital clinic.—I am, etc.,

London, S.E.16. KENNETH CAMERON.

Prolonged, Close Caging

SIR,—Friends in the United States have asked us to obtain, as a matter of urgency and for submission to a congressional committee, authentic information as to the technical effects on laboratory dogs of close and prolonged caging. The Food and Drug Administration is carrying out long-term toxicity tests of aniline and other colourings used in human food, and for this

purpose beagles are housed, from the age of three months, in cages measuring approximately 30 in. by 36 in., in which they remain for two and a half to three years, the cages being washed down without removal of the dogs. It is claimed that the provision of exercise runs, even if these were uniform in construction and use, would impair the validity of the tests, the results of which will be applied to human beings living under more normal conditions.

We should be most grateful if any of your readers could supply us with any information bearing on the methodological aspect of prolonged and close caging.—I am, etc.,

C. W. HUME.
Secretary-General,
The Universities Federation for Animal Welfare.

Thyroid Disease

SIR,—I was interested to read Professor E. J. Wayne's Lumleian Lectures on "Clinical and Metabolic Studies in Thyroid Disease" (*Journal*, January 2 and 9, pp. 1 and 78).

My patient, a lady aged 37, underwent a subtotal thyroidectomy on October 5, 1959, for thyrotoxicosis (her clinical index being about 37). On November 18 she complained of heaviness of her arms and a "pins-and-needles" sensation in both hands and fingers. On examination the paraesthesiae were confined mainly to the median nerve areas. She presented no signs of hypothyroidism, and there were no objective changes detectable in the nervous, muscular, or vascular system to account for her symptoms. About a month later, however, the patient exhibited the more widely recognized features of a hypothyroid state. She is now completely symptom-free following the commencement of an oral thyroid preparation.

This case is of interest in the fact that the patient was initially extremely "toxic"; she then exhibited the signs and symptoms of a hypothyroid state following subtotal thyroidectomy, which presented with the paraesthesiae in the upper limbs. These symptoms were the first to disappear after commencing replacement therapy. I am grateful to Professor Wayne for enabling me to appreciate this unusual early presentation of hypothyroidism.—I am, etc.,

Bracknell, Berks. I. G. ROSS.

Munchausen Syndrome

SIR,—I should like to record an example of the Munchausen syndrome which has not been mentioned in your columns. The investigation of this man's complaints could prove costly, and he is aggressive and truculent in his behaviour during admission. I feel that he should therefore be brought to the notice of casualty officers and house-physicians.

His name is Charles P. and he gives his age as 70. He is a Northcountryman who claims to have worked as a coal-miner for 42 years. He presented in casualty with a slightly unconvincing description of myocardial infarction, and following admission to the ward added the classic symptomatology of thyrotoxicosis to his previous history. He claimed to have a lump in his throat which made his eyes pop out (*sic*), and gave a description of thyroid function tests and treatment with "neo-mercazole" (*sic*) which had been given in another hospital. Despite this statement, he had initially denied any other hospital attendance for 35 years. In this and other matters he was inconsistent and showed considerable variation in his answers to direct questions.

There were no symptoms other than those of his two main complaints, but his past history included numerous operations. On physical examination, there was little abnormality. There were a number of recent puncture marks in both deltoid areas, and the veins in his antecubital fossae had obviously been punctured on numerous occasions. He had the following scars on his abdomen and chest wall: right lower paramedian, cholecystectomy, empyema, and a scar or two over both kidneys posteriorly. He had warm hands, a regular tachycardia, inconsistent lid lag, and showed hyperkinetic movements. From the manner in which he gave this history, and absence of convincing physical signs, it was felt that he was an example of the Munchausen syndrome. It was not possible, however, to exclude a mild thyrotoxicosis, and it was decided to perform a radioactive iodine test. During his hospital stay of four days he was evasive, suspicious, and aggressive. Following his exposure as a Munchausen case during a ward round, he became extremely violent and threw numerous objects.

Diagnostic radioactive iodine was given, but he discharged himself before all the results were obtained. The first two urine specimens were compatible with a diagnosis of thyrotoxicosis. He was seen by a psychiatrist, who felt that he was a typical example of the Munchausen syndrome. Charles P. told the psychiatrist that he normally worked the West Country, but came up to London in the winter because it was warmer. He has, to our certain knowledge, been seen in at least four other hospitals. In three of these he gave a similar description of chest pain, but added the story of thyrotoxicosis on only two occasions. In 1950 a Charles P., with identical abdominal scars, presented at a Wigan hospital with a story of renal colic. No abnormality was found on investigation, and he took his own discharge. It is therefore possible that he may change his story from time to time.

After his discharge from this hospital he was admitted to a near-by hospital following presentation with chest pain and thyrotoxic symptoms. During his admission he also added the classical symptoms (but not signs) of glaucoma.

—I am, etc.,

Hammersmith Hospital, London, W.12. NEIL MCINTYRE.

Behind the Depressive Syndrome

SIR,—While agreeing with the broader implications of Dr. John Cleobury's letter "Behind the Depressive Symptom" (*Journal*, January 16, p. 203), there is one view expressed which I feel needs comment. He considers the endogenous depressions precipitated by stress should properly be included in the "minority group of cases" described by Professor Martin Roth in the syndrome named by him the "calamity syndrome" (see *Journal*, February 28, 1959, p. 579). If Dr. Cleobury re-reads this account, or even better reads the more expanded report,[1] he will appreciate that the symptoms at the core of this state are depersonalization and phobic anxiety. Such depressive features as commonly co-exist exhibit the features usually attributed to "neurotic" depression. The condition not only fails to respond to E.C.T., but is frequently worsened by this treatment.

With regard to the pattern of previous personality traits and *specific* precipitating events, as well as its clinical features, this newly defined syndrome forms a distinct entity, and it merely confuses this new-found clarity to group with it a completely different disorder solely on the grounds that both illnesses are precipitated by stress. Why stop there? Why not include *all* psychiatric disorders precipitated by stress into one mammoth group and throw it back into the melting-pot?

I would further hesitate to say the state constitutes a "minority group," for at the University Department of Psychiatry in Newcastle 135 cases were seen in well under two years. Our finding there was that, whereas in all neuroses females preponderate in the ratio of 3 : 2,

when this calamity group—which is commonest in young married women—is extracted one finds the ratio in the remaining neurotics to be two females to three males. It is a common condition previously unrecognized, cases having been classified according to the predominant secondary symptoms.—I am, etc.,

St. James's Hospital, Leeds, 9. J. CRAWFORD LITTLE.

REFERENCE

[1] *Proc. roy. Soc. Med.*, 1959, **52**, 587.

Chronic Disablement from Neurological Disorders

SIR,—Your annotation on chronic disablement from neurological disorders (*Journal*, January 2, p. 45) has elicited interesting letters from orthopaedic and geriatric hospitals (*Journal*, January 16, p. 195). The Oxford Geriatric Unit for the last five years has cared for the young disabled men and women in the cheerful atmosphere of Rivermead Hospital, which also serves as a geriatric rehabilitation unit.

All grades of disability can be treated, from permanent in-patient care for the more severely disabled, to those who are fit and able to live at home and attend as day-patients. Some patients alternate between staying at home and staying in hospital, in all gradations, from an occasional day at home to a fortnight in hospital to ten weeks at home. Physiotherapy and occupational therapy are provided, and the closest contact is kept with relatives and friends. The latter is not possible in any institution, however well run, which takes patients from a distance. Close contact is kept with the patient's general practitioner and with the psychiatrist, physician, or surgeon who attended him at the onset of his disability. We also have maximum support from the local authorities, the Ministry of Labour, and the National Assistance Board.

Mr. P. S. London (*Journal*, February 6, p. 428) mentioned the increasing number of disabled survivors of severe head injuries. This is also our experience. However, two young men who had sustained severe head injuries and been unemployed for over three years before attending here have been placed in full employment, though both are hemiplegics and one has marked aphasia.

We have been so impressed by the number of patients who, after appropriate treatment, can return into the community to earn an economic wage, that a technical rehabilitation officer is now engaged in assessing industrial competence. My practical experience over the last five years has convinced me that the early labelling of patients as incurable is always unwise and often inaccurate. Appropriate and often lengthy rehabilitation must be undertaken before consigning them to perpetual institutional care of whatever excellence.—I am, etc.,

Rivermead Hospital, Oxford. CELIA WESTROPP.

Towards Clean Air

SIR,—It has been held since the time of Virchow that non-specific chronic irritation may play some part in the genesis of cancer, and this belief is supported by recent experimental work.[1] The letter from Mr. R. E. Waller and Mr. B. T. Commins (*Journal*, February 6, p. 423) can therefore be only partially reassuring in view of the fact that substitution of smokeless fuels for coal can at present do nothing towards the elimination of sulphur dioxide from the atmosphere.[2]—I am, etc.,

Department of Experimental Pathology and Cancer Research, School of Medicine, Leeds, 2. T. D. DAY.

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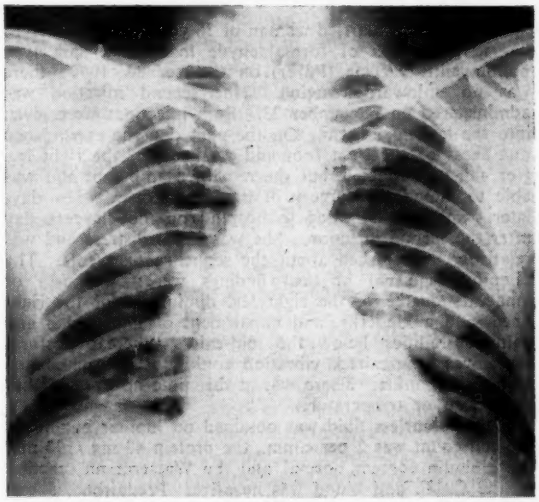
[1] Menkin, V., *Cancer Res.*, 1959, **19**, 544.
[2] Thring, M. W., *Air Pollution*, 1957, p. 6. Butterworth, London.

Cadmium Poisoning

SIR,—I was very interested to read the report of a case of acute cadmium poisoning by Dr. D. M. Evans, of the Atomic Energy Authority, Aldermaston (*Journal*, January 16, p. 173). This recalls a similar case seen in 1955, which concerned a man of 49, overcome by fumes while torch-welding parts of an aircraft in his own small workshop, not equipped with any form of forced extract ventilation.

Cadmium is frequently used for coating metal surfaces to prevent corrosion, and the danger of hot-welding without preliminary removal of the cadmium coat is well understood. This is usually done by preliminary sand-blasting, which our patient neglected to do owing to the urgency of the repairs. Within a short time he developed an intense burning pain behind the sternum and in both sides, with violent cough and vomiting. These symptoms gradually wore off within the next few days, and when I saw him eight days later he was already much improved but still short of breath and very anxious. There were no abnormal physical signs in the chest, but a radiograph (see Fig.) showed diffuse soft mottling in both lungs suggestive of an acute inflammatory reaction or pulmonary oedema. Within three weeks most of the soft mottling had cleared and the patient was free of symptoms.



Radiograph of chest, showing diffuse soft mottling of both lungs.

When the case was reported at the time to Dr. Donald Hunter, of the London Hospital, he agreed that this appeared to be a clear-cut example of acute cadmium poisoning.—I am, etc.,

Central Chest Clinic, Reading. A. J. KARLISH.

Psychogenic Disorders in Children

SIR,—Of the interesting issues raised by Dr. Stanley Ellison (*Journal*, February 6, p. 424), I would comment on but two: the role of the general practitioner in the psychosomatic disorders of children, and the functions of a paediatric department. That the family doctor "should, as a doctor, undertake the continual medical care of children" is of course highly desirable, and is in fact done in varying degrees. With "psychosomatic orientation" he could, and sometimes does, deal most effectively with the emotional disorders of children.

particularly in the beneficial early stages. As this practice spreads fewer such children will be sent to the paediatrician.

The work of a paediatric department is largely determined by the demands of the general practitioner. There is some distortion of reality when general practice and paediatrics are made to appear as interchangeable disciplines. The practitioner can because of the relationship which exists in practice between doctor and patient provide a service denied to the paediatrician. The paediatrician, by his particular training, experience, and specialization, can provide a service of special help to the family doctor to augment his work. It is surely not a competitive activity, as Dr. Ellison implies, but one of mutual assistance for the benefit of the patient.—I am, etc.,

London, W.1. DAVID MORRIS.

Temporary Paralysis After Polio Vaccine

SIR,—Following the report of a case of temporary paralysis after poliomyelitis vaccination by Dr. M. S. Sabour (*Journal*, November 14, 1959, p. 1021), we are prompted to record a similar occurrence.

The patient, a married woman of 26 years of age, received her first injection of formaldehyde inactivated Salk type poliomyelitis vaccine (Pfizer) on October 24, 1959: there was no untoward reaction. Her second injection was administered on November 23. Both injections were given into the left upper arm. On the next day she experienced numbness of the right foot and weakness of the right leg. Her gait was affected, but she remained ambulant and was able to attend the surgery of her practitioner a few days later. She was admitted to hospital on the eleventh day after the second injection. She was in no distress and was relatively unperturbed about the sequence of events. The essential abnormal physical findings were: weakness of moderate degree of the right leg, diminution of the right knee- and ankle-jerks, and impairment of light touch and pain sensibilities below the mid-calf. Whereas postural sense was unimpaired, vibration could not be appreciated at the right ankle. There was at this time no upset of her pulse rate or temperature.

Clear colourless fluid was obtained on lumbar puncture; the cell count was 2 per c.mm., the protein 40 mg./100 ml., the globulin content normal and the Wassermann reaction of the C.S.F. and blood was negative. Prednisone, 5 mg. thrice daily, was prescribed, the dose being "tailed off" after 10 days. When last seen on January 27 the muscular weakness was much less evident, the sensory features had cleared, but the deep reflexes were still diminished in the right leg.

The virological department of Pfizer was approached but could find no record of a similar type of reaction either in this country or in the United States, and expressed the opinion that, in the absence of virological investigations, the condition should be regarded as coincidental and not attributable to vaccination. No cases with similar neurological lesions have been encountered in the Burnley area in recent months. In explanation of Dr. Sabour's case, Dr. A. Griffiths (*Journal*, December 12, p. 1333) suggested the diagnosis of allergic radiculitis. However, if he is correct in his assumption that in this type of serum reaction the brachial plexus is always involved, it would fail to explain the distribution of the signs in our own case. Allergic reactions to Salk vaccine have been reported—rhinitis, asthma, arthralgia, and skin lesions—and the penicillin content has not been considered to be responsible.[1] Kaufman and Janaway[2] describe a severe allergic reaction: marked urticaria, fever, leucocytosis, arthralgia, myositis, and radiculitis developed after the third injection of poliomyelitis vaccine. The neurological findings were weakness of the left arm, slight winging of the left scapula, diminution of the biceps reflex, and hypalgesia over the outer aspect of the left forearm. Complete recovery ensued. The offending substance could not be identified. Direct and passive transfer tests with streptomycin, penicillin, horse serum, and vaccine were negative, as were precipitin tests against monkey-kidney and horse-serum antigens; the possibility of silk antigen—from silk filters—was also excluded.

The infrequency of reactions to poliomyelitis vaccine should be stressed.—We are, etc.,

J. SHAFAR.
J. P. MIDGLEY.

Burnley General Hospital, Lancs.

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[1] Crepea, S. B., *J. Allergy*, 1957, **28**, 262.
[2] Kaufman, R. E., and Janeway, M., *N.Y. St. J. Med.*, 1958, **58**, 2382.

"Emergency Ward 10"

SIR,—May I raise yet another protest against the television programme, "Emergency Ward 10"? Of its possible advantages I cannot be convinced, and the disservice it does to patients, potential and actual, and to us who have to advise and treat them, is only too apparent. I will give but two recent instances. First: a small relative asked to see an operating theatre, and I allowed her to look into an unoccupied one. She took a long look and then said in a relieved tone, "But it's not frightening at all. In the telly it was dreadful." Again: I saw a woman with a foetal adenoma of the thyroid and told her that surgical removal was advisable, and indeed the only treatment. Her reply was, "Could I not have some radium fluid injected into my veins?"

I need not comment. But I would point out that programmes of this kind cannot be given without the help of medical collaborators. How can they justify themselves?—I am, etc.,

Hove. C. M. OTTLEY.

Peak-flow Meter

SIR,—We are grateful to Dr. D. V. Bates for his kind remarks (*Journal*, January 2, p. 56), but we are sorry to hear that he feels, from his study of the literature, that the peak flow may prove to be a "very insensitive" index of ventilatory capacity. The article by Dr. W. Lockhart and others in the same issue (p. 37) and the letter from Dr. Francis Prime (*Journal*, February 6, p. 423) seem to be a more effective answer to this suggestion than any that we could make, but it may be of interest to consider how this conflict of opinion can have arisen.

(1) As we indicated in our paper (*Journal*, November 21, p. 1041), all previous measurements of the peak flow in the literature gave considerably lower figures in normals than we found, especially when a small model of the Lilly pneumotachograph was used. As we pointed out, this leads to difficulty in distinguishing normals from abnormals and is probably one of the main reasons which led Bouhuys, in the paper cited[1] by Dr. Bates, to reject the peak flow as an index of ventilatory capacity.

(2) In the last analysis, the real value of such an index can only be judged clinically. Its relationship to other indices is of relatively little interest because no two of these indices are sufficiently closely correlated for any kind of factor to be used to translate one into the other *in the individual case*, which is what matters in clinical practice.

Similarly, *a priori* speculation about the physiological mechanisms underlying the index, though fascinating, is a poor basis from which to predict its likely usefulness, and is valueless compared with practical experience. Such experience is almost impossible to obtain on a sufficiently wide scale under clinical conditions without an instrument which is really portable and easy to use.

A number of people have now obtained this experience, and we suggest that their opinion is to be preferred to that of those who have only carried out relatively small-scale experiments in the laboratory with rather unsatisfactory apparatus.—We are, etc.,

B. M. WRIGHT.
C. B. MCKERROW.

National Institute for Medical Research,
London, N.W.7.

REFERENCE

[1] Bouhuys, A., *Acta med. scand.*, 1957, **159**, 91.

Internal Tampons

SIR,—I attended a nice little girl to-day, aged 15, for vague genital pain. She was only a child, though she strove to be nonchalant like the Brave New World. I thought her trouble might have been due to the chafing of the diaper, as she had heavy periods. But she answered me No—" because I use internal tampons. All the girls at school use them and the mistress says it's quite all right." She then proceeded to show with pride and trepidation an example of the article she was using.

Surely, Sir, instrumentation of this sort is harmful in two ways at least: (*a*) psychologically for obvious reasons, and (*b*) physiologically ditto. Surely also it is a complete negation of one of the cardinal principles of surgery, i.e., to provide free drainage.

I still meet in this enlightened era of welfare in general, and " guidance " clinics in particular, the unhappy child with a running ear whose mother has plugged it with wool, and sometimes I discover a pledget of wool that has lain stinking in the meatal canal for months. In my opinion the internal tampon should be classed as a dangerous appliance, not to be sold on demand over the counter at all and only to be prescribed on an E.C.10 for a very special occasion, as, for example, for an acrobat or knock-about dancer, whose livelihood might otherwise be at stake.—I am, etc.,

Buxted, Sussex. W. R. E. HARRISON.

SIR,—Yesterday I removed my second forgotten internal tampon (" tampax ") which had remained *in situ* for five days, and which had sent the patient to me complaining of a faint discharge. The first forgotten tampon removed by me must have been *in situ* for several weeks, because the discharge was powerfully malodorous and douching by the patient had failed to clear it up. I found this tampon folded high up in the vaginal vault and the liquid contents dammed behind it were indeed most offensive.

I write this note because practitioners vary in their attitude and treatment of vaginal discharges from (*a*) Referral to a gynaecologist (this may take weeks and prolong and intensify damage). (*b*) Referral to the V.D. clinic. The patient may object to this, but if she goes attention will be received sooner—that is, within a week. (*c*) Put off vaginal examination and order further douching or self-insertion of chemical pessaries—both obviously useless when the cause is just begging to be removed.

The possibility of further complications developing in the form of salpingitis and tubo-ovarian abscess is worth remembering. Furthermore, we live in an age when high-pressure advertising suggests that it is only necessary to cover up the odour ! " Somebody isn't using ——." Both my patients expressed surprise that they had fitted and forgotten their internal tampon.—I am, etc.,

Slough. N. C. HYPHER.

Dog-bite Wounds

SIR,—In their article (*Journal*, January 16, p. 169) Mr. M. L. H. Lee and Dr. A. J. Buhr recommend prophylactic penicillin therapy in serious dog-bites in cases of infection with *Pasteurella septica*. Could the recommendation be extended to cat-bites ? A few years ago a man had occasion to take a small, injured cat for destruction to the R.S.P.C.A. He put it in a sack, but he was so sorry for it that he left its head out, and it bit him. A few days later he came to the casualty department of the West Wales General Hospital with a very " nasty " septic finger and red streaks of lymphangitis running up his arm. There were some unusual characters about the lesion, a swab was taken, and he was admitted immediately. *Pasteuralla septica* was grown. In this case it was his own kind heart and lateness in reporting that led to the seriousness of the lesion, which, I believe, led to permanent deformity ; but, if he had been seen early, how many of us would have given him prophylactic penicillin ?—I am, etc.,

St. David's Hospital, Carmarthen. A. R. KEMP.

SIR,—Mr. J. E. Smith in his letter (*Journal*, February 13, p. 499) indicates the relative frequency of *Pasteurella septica* infection following cat-bites. During the review by Dr. A. J. Buhr and myself (*Journal*, January 16, p. 169) of dog-bites, eight cat-bites which had been examined bacteriologically during the same period were analysed. None of the bites were sutured. Seven became infected, four with *Past. septica* (in pure culture or in association with micrococci or α-haemolytic streptococci). The other three infected bites cultured (*a*) *Neisseria*, (*b*) *Pseudomonas pyocyanea* and *Proteus mirabilis*, (*c*) no growth. The non-infected bite was sterile on the day of first attendance, and was the only cat-bite to receive prophylactic penicillin. All healed in nine days or less except for one bite (*Past. septica* with micrococci) which took 30 days and another (*Past. septica*) that took 44 days to heal.—I am, etc.,

Nuffield Department of Orthopaedic Surgery, Oxford. M. L. H. LEE.

A Cautionary Tale

SIR,—Medical practice is seldom lacking in surprises, and the pathway of prognosis is treacherous. Most errors occur when giving a bad prognosis. The average practice includes several octogenarians who claim they were not expected to reach 20, but survived to see successive medical advisers precede them to the grave. Patients naturally derive a solid satisfaction in defeating " medical science," and an exploded prognosis can, in such cases, act as a strong tonic.

A patient, a single man now aged 40, first consulted me in 1949. He had lost all his hair at the age of 4, and, although a slight regrowth occurred when serving in India in his twenties, it all dropped out again in 1947. On examination there was a complete loss of hair, including eyebrows, beard, axillary, and pubic distribution. He never

had to shave. Even with a strong magnifying-glass there was not a sign of hair anywhere. I felt nothing could be done for him, and advised him not to waste money answering advertisements in the press. From time to time he reappeared armed with articles from the various *Digests* and national dailies reporting remarkable cures in similar cases. After a show of resistance on my part I generally had to prescribe a course of the latest wonder-drug, but always to no avail. Not even an ultra-violet lamp (free of purchase tax), which we thought might reproduce the favourable conditions of India, succeeded in growing a single hair.

In 1955, feeling in need of support, I sent him to a consultant, who advised him "to try to develop a philosophic attitude to his disability, and to seek a wider social life with view to matrimony." This echoed my sentiments exactly. For some time there was peace (undisturbed by matrimony).

In January, 1959, the tidings of cortisone reached him, and the inevitable visits restarted. I again repeated the hopeless prognosis, and stressed the futility of further experiments and the danger of steroid treatment. However, he worried me until I sent him to a dermatologist with a letter more remarkable for apologies than clinical data. Two weeks later he reported that he had started treatment, and that the consultant thought there was a good chance. I told him quite frankly that I thought he had misunderstood what the consultant had said. The next day I received a letter stating that steroid treatment had started.

To my amazement in five weeks hair was sprouting widely, and in two months he had a good growth. In three months he had a mop of hair of which anyone could be proud, together with eyebrows, axillary, body, and pubic hair, and the need to shave four times a week. Now, after eleven years of maladjustment to alopecia universalis, he cycles past me in the street with his hair streaming in the wind and a seraphic smile from ear to ear.

But a question arises to which I can see no wholly satisfactory answer. Up to date I have issued prescriptions for about £80 worth of the recommended steroid. The total cost is probably greater, as the preparation was dearer a year ago than it is now. Taking the reduced dose of two tablets a day, it will cost about £50 a year to maintain this ecstatic state. As a scientific achievement it is certainly worth the money, but can the Welfare State afford it? What is the ceiling price for a man's head of hair? The mind boggles at the prospect of what may happen if a similar treatment is discovered for the partially bald. Which political party will risk losing half its electorate by legislating on the price of baldness? How much can the State afford for aesthetic prescribing, bearing in mind that hospitals are waiting to be built and most aspects of the National Health Service (including doctors) are frustrated for the want of money? Where shall the line be drawn?—I am, etc.,

Sheffield, 8. E. C. ATKINSON.

Space Travel

SIR,—While Dr. A. J. C. Tingey's comments (*Journal*, February 13, p. 504) on sterilization of space vehicles are timely and to the point, he is, I venture to suggest, a little too sweeping in saying "it would therefore be prudent to discourage all projects for space travel until a tentative scheme has been evolved to cope with consequences of a dangerous nature."

He will recall that at the usual atmospheric re-entry speed of some 16,000 miles/hour (25,750 km./hour) the external surface of the vehicle is heated to a temperature of some thousands of degrees centigrade, sufficient to sterilize this surface. Further, any contamination of the interior of the ship appears of significance only when this has been derived from Mars or Venus, as our nearest satellite in space and that to which our immediate "there and back" attempts will be directed is of course the moon, whose surface is subjected to heavy primary cosmic-ray bombardment, rendering it sterile.

It is not inconceivable that the heat engendered by atmospheric re-entry may be utilized to sterilize equipment, space suits, etc., which may have made actual contact with "foreign" soil and that personal disinfection may never be required as at no time will there be direct (that is, surface-to-surface) contact of the traveller with his new environment, but only indirectly behind protective apparel. Even the atmosphere breathed by the astronaut will of course be made on earth and transported with him.

In a different category, however, are the harmless commensals of man and non-pathogens which may mutate into violent forms under the influence of radiation insufficient in strength to affect man but sufficiently powerful to interfere with bacterial antigenic structure and reproduction. This I think is the real hazard, the effect of ionizing radiation upon known viruses and bacteria. We do not have to postulate a Venusian staphylococcus or a Martian coliform.—I am, etc.,

Lytham St. Annes, Lancs. J. R. BROWN.

Quiescent Malaria Parasites

SIR,—In a London hospital recently a female patient developed *P. falciparum* malaria following a blood transfusion. The donor was a 19-year-old Nigerian medical student who arrived in this country from Lagos less than six months before acting as a blood donor. The malaria infection in the recipient was a relatively severe one and 3% of her erythrocytes were parasitized. The search for parasites in thick blood films of the donor failed to reveal any parasites within the time usually allotted to examinations of this kind, and, but for the fact that the blood was known to be infective, a negative finding would have been returned. When a second thick film was examined, one mature female gametocyte (crescent) was found, but no trophozoites. Following the examination of further thick films, two or three typical merozoites of *P. falciparum* were seen and, rather surprisingly, scanty schizonts of *P. malariae* (quartan). It is estimated that at least three hours of microscopy were necessary before a positive finding was obtained.

While this investigation was in progress it came to our notice that a young Nigerian boxer had died following a knock-out blow in the ring at Wolverhampton. He also had been in this country only two and a half months previous to his death. Through the courtesy of Dr. A. G. Marshall, pathologist at the Royal Hospital, Wolverhampton, some post-mortem material, spleen and blood smears, was obtained. After a prolonged search of the blood smears three typical ring forms of *P. falciparum* were found and scanty malarial pigment was found in sections of the spleen, even though this organ was not enlarged and weighed only 156 g.

It has often been demonstrated that the blood of many young negroes and adolescents of both sexes harbour malaria parasites when they first arrive in this country from holo-endemic malarious areas, and especially for the first six months. It is not known how long parasites are able to survive in the human host in the absence of reinfection, in the absence of antimalarial drugs being given, and when the carrier is living in a temperate region. However, based on what we know from our studies of

malaria therapy, the longevity of malaria parasites varies considerably according to the species involved: *P. falciparum*, six months to one year; *P. vivax*, one to three years; *P. malariae*, twenty years or longer. This represents the time since the individual was last infected by the bite of a mosquito.

Because malaria is being eradicated or brought under control in some parts of the world, it does not follow that the percentage of indigenous adolescents who are carrying parasites has been appreciably reduced, especially in areas where control has been restricted to interrupting transmission by anti-adult-mosquito work. In a few places where control, combined with mass drug therapy of the human population as well as anti-mosquito operations, the incidence of parasitaemia would, of course, drop appreciably.

The problem of healthy carriers entering this country is not of any great epidemiological significance, because, having reached a degree of immunity or premunition, very few, if any, would develop gametocytes or be likely to develop severe overt fever. Also, based on laboratory and field experiments, our indigenous *Anopheles atroparvus* is resistant to infection with tropical African strains of *P. falciparum*, although it is highly susceptible to eastern European strains of the same species.

Many negroes in their late teens or early twenties who come to this country from malarious areas to work or to become professional athletes such as professional boxers will undoubtedly be harbouring malaria parasites for months or years according to the species of parasite involved. Boxing promoters, and even officials of the British Boxing Board of Control, may conceivably be unaware of this state of affairs. Knowing how careful the Board of Control is in looking after the welfare of young boxers, they would, if they knew, take any necessary measures to ensure that no young negro boxer entered the ring handicapped by a hidden enemy, the malaria parasite and, in consequence, some degree of anaemia. Some suggestions which may be helpful are:

(1) Every negro boxer on entering this country from a malarious area should have a haematological examination.

(2) Thick and thin blood films should be examined for malaria parasites, especially during the first few months after entering the country.

(3) All teenage negro boxers from malarious areas, on entering this country to practise their profession, should be advised to take a course of antimalarial drugs, whether or not malarial parasites have been found.

(4) The spleen should be carefully palpated by a competent authority, and, if found to be much enlarged, the boxer should be refused permission to enter the ring pending an improvement.

—I am, etc.,

Malaria Reference Laboratory, Horton Hospital, Epsom. P. G. SHUTE.

Conservative Treatment of Ulcerative Colitis

SIR,—Anyone who has seen the occurrence of cancer in medically successfully treated ulcerative colitis will wonder whether any more cases should be left to the physicians. One of the difficulties of general practice to-day is to overcome the, to me, inexplicable reluctance to operate. I wonder whether it would not be wise to operate at once on all established ulcerative colitis, even in children.

It would be interesting to have the views of the experts on this very important matter.—I am, etc.,

London, N.W.4. R. W. COCKSHUT.

Polio Risk to Europeans in the Tropics

SIR,—Professor Harold Scarborough's letter on the risk of paralytic poliomyelitis to visitors to Nigeria (*Journal*, February 20, p. 570) is too limited in its scope. Our teaching in this hospital has always stressed the supreme importance of paralytic poliomyelitis in Europeans in tropical climates. It is generally recognized that, since the introduction of "paludrine" (proguanil hydrochloride), the greatest risk to which the European is exposed anywhere in the tropics is paralytic poliomyelitis. There can be few of us with much experience in the tropics who have not lost dear friends, relations, or colleagues from that malady.

The Services and the Colonial, Foreign, and Commonwealth Relations Offices have for some time past provided inoculations with subsequent booster doses for all personnel and their families in tropical countries from the exiguous supplies of vaccine available. Missions and commercial firms have been helped to the limit of our capacity in the past two years. Fortunately the improved supply position does away with the hitherto invidious task of refusing the vaccine to deserving travellers without a "permit" and enables all who are going to the tropics—even on a short visit—to receive this most necessary inoculation.—I am, etc.,

Hospital for Tropical Diseases, University College Hospital, London, W.C.1. GEORGE R. MCROBERT.

Be My Valentine

SIR,—I suppose many of us are slowly succumbing to the ever growing volume of advertising material. Fascination follows bewilderment as the propaganda becomes multicoloured, transparent, circular, figured, and more recently elongated.

Now we are not only assailed by shape and colour but also by monotonous repetition of chosen phrases and slogans. All this of course is the pattern that has successfully sold soap-powder and toothpaste—we are simply the latest target. But surely a new low in advertising technique has been reached when we are sent mock Valentine cards and invited to rearrange anagrams to form the name of a firm's products in order to win a prize?

Perhaps if more doctors would use the postcard—as I have done—to ask the firm to remove my name from their mailing list we might ultimately command more respect as a profession.—I am, etc.,

Liverpool, 8. CYRIL TAYLOR.

POINTS FROM LETTERS

Identification of Tablets

Mr. A. PIRNIE, B.Pharm. (Army School of Dispensing, Aldershot), writes: I was interested in Dr. J. D. W. Whitney's article (*Journal*, January 2, p. 50) pointing out the need for a system of tablet identification and the proposals made. Some time ago I discussed with a pharmacist colleague the possibilities of a scheme involving a similar principle of die-stamping with letters and digits related to a code-book. The idea I had in mind was suggested by the system used for car registration numbers, which provides, without using more than three letters *drawn from the whole alphabet* together with up to three digits, sufficient combinations to identify every known tablet formulation and every new or changed formulation for very many years to come.

In this way it would be possible to ignore the use of initial letters associated with pharmaceutical firms or such works as the *B.P.*, *B.P.C.*, *B.N.F.*, etc. This information, together with all essential details concerning the nature of the tablet, should be shown in the code-book under its identity number.

Obituary

WILFRED HARRIS, M.D., F.R.C.P.

Dr. Wilfred Harris, consulting physician to St. Mary's Hospital and to Maida Vale Hospital for Nervous Diseases, died at his home in London on February 28. He was 90 years of age. One of the earliest teachers in the specialty of neurology, he carried out much notable research, especially into methods of relieving pain.

Wilfred John Harris was born in Madras on December 2, 1869. He was the third son of William Henry Harris, M.D., I.M.S., of Viveham, North Devon. At the time of his birth his father, who had studied medicine at the London Hospital, was professor of midwifery and the diseases of women and children at Madras and was later responsible for the novel pavilion-style of the Maternity Hospital at Madras which was opened in 1880. A veteran of the Crimea and the Indian Mutiny, he retired from the Indian Medical Service with the rank of deputy surgeon-general.

[*Lafayette, Ltd.*

Wilfred Harris was educated at Sherborne School, University College School, and Gonville and Caius College, Cambridge. Awarded a university scholarship in medicine at St. Mary's Hospital, he graduated M.B., Ch.B. in 1894, and after holding house appointments at his teaching hospital he spent two years as a resident at the National Hospital, Queen Square. Admitted M.R.C.P. in 1896, he proceeded M.D. in 1898. He had not, however, severed his connexion with St. Mary's, the hospital with which the greater part of his career was to be identified, and he accepted the post of junior medical tutor there. For some years a small department in the hospital had been devoted to the electrical treatment of disease, and in 1899 Harris was invited to take charge of it with the title of "electrotherapeutics officer." Four years later he sought permission to convert it into an out-patient clinic for nervous diseases, and in 1907 a department of neurology—the first in any undergraduate teaching hospital—was formally established with Harris as the first lecturer.

In spite of his later appointment to senior hospital posts and to the wider responsibilities which they involved, he continued his weekly neurological clinics until his retirement in 1935 and returned to take charge of the department during the second world war while his successor was serving with the Royal Air Force. He had been elected F.R.C.P. in 1905, the year in which he was appointed physician to St. Mary's, and he was later an examiner in medicine for the Royal College of Physicians, the University of Durham, and Cambridge University. During the first world war he served as neurologist to the 3rd London General Hospital, and in 1917 he was Arris and Gale lecturer at the Royal College of Surgeons. Another hospital appointment he held was that of consulting physician to the London Chest Hospital.

When, in 1919, the University Grants Committee financed chairs in medicine and surgery at four of the London medical schools, St. Mary's was not one of those favoured, but the dean decided nevertheless that clinical units in medicine and surgery should be established at the school. Funds were not available for chairs, but Harris accepted the post of director of the medical unit on a part-time basis. The respect which his work was accorded among British neurologists was reflected by his election as president of the Section of Neurology of the Royal Society of Medicine, as first president of the Association of British Neurologists (from 1933 to 1936) and as president of the British branch of the International League against Epilepsy.

Harris was the author of several books and nearly 200 papers, his first appearing in 1896. While in his eighties he contributed several important papers to this journal, the last being entitled "Evolution of Binocular and Stereoscopic Vision in Man and Other Animals." His early appreciation of the clinical importance of shock is evident in his monograph, *Nerve Injuries and Shock* (1915), while more than twenty years of study and research went into the work on *Neuritis and Neuralgia* (1926). It was in 1909 that he had conceived the idea of injecting alcohol into the Gasserian ganglion for the relief of trigeminal neuralgia, and he developed this procedure to a stage of technical perfection which was unsurpassed. It was a delicate operation requiring extreme precision and the most accurate and detailed anatomical knowledge, and Harris perfected his technique by hundreds of trials in which he used methylene blue, studying the distribution after dissection. When he was very much older and his hand might well have lost some of its skill he was able to amaze a large international gathering of neurologists by his unwavering finesse and accuracy in demonstrating his technique. His remarkable anatomical skill was also in evidence in his book on *The Morphology of the Brachial Plexus*, published in 1939, when he was 70. Harris was well known at the prosectorium in the Zoological Society's Gardens in Regent's Park. He began his studies there in 1902, and only a few years ago he was investigating the optic tracts of the chameleon and the octopus.

His renown as a teacher was not unconnected with his own high standards and the corresponding demands which he made of his students. Although the remarkable advances in neurophysiology in the 1930s marked him off as the exponent of an older school, he had always shown no lack of originality in his own work, and he was one of the first to employ the cinematograph in medical teaching, which he did as early as 1909 for demonstrating certain cases of nervous disease.

One of Harris's great interests was the collection of early English silver spoons, a hobby which he took up when only 18. At the dinner held at St. Mary's to celebrate his 80th birthday, the gift to him by his colleagues of two spoons for his collection was obviously one which touched him deeply. His collection of 80 choice specimens was sold at Christie's in 1957 and fetched no less than £14,876. Among them was an Edward IV spoon of 1463 which is probably the earliest example of English silver bearing a date letter; it was bought for £1,600, a record price for any spoon. His interest in other types of antique craftsmanship is witnessed by his presentation to Caius College of an antique mahogany clock made by Tutet in 1765.

Dr. Harris married Mabel, the eldest daughter of Rear-Admiral Richard Mayne, C.B., M.P., and she and two sons and a daughter survive him.

DR. DENIS BRINTON writes: Wilfred Harris kept his interests in neurology and in St. Mary's Hospital medical school so fully alive until within so short a time of his death that it is extraordinary to think that he retired twenty-five years ago. But even this statement needs qualification; for, when his successor was called up at the beginning of the second world war, Harris characteristically returned to St. Mary's and continued with the ordinary work of a busy neurological department for the next six years. Teaching was always a joy to him and to those he taught.

Shortly after the first war he had played a considerable part in the foundation of the professorial medical unit at St. Mary's, and was indeed in charge of it as a temporary measure. When the first full-time professor was appointed,

Harris unselfishly surrendered for the use of this unit the greater part of the beds to which he was entitled as a senior physician, retaining only the few that were necessary for the formation of a neurological department. His contributions to neurology were many, but were particularly fruitful in the field of the peripheral nerves. His work on the cranial nerves, especially the trigeminal, is well known. His knowledge of the brachial plexus was unique; and, in 1939, he published a fascinating book on its comparative anatomy, founded on his personal dissections at the Zoo.

Even after the end of the second world war Harris frequently attended the clinico-pathological discussions at St. Mary's Hospital, and for a number of years gave a lecture arranged to coincide with his birthday. His interest in the activities of the students of the medical school continued well into his ninth decade. It is not so long ago that he was last seen at a hospital rugger match.

An exacting master, who always insisted on the greatest effort from his subordinates, he will be remembered with deep affection by all those who worked with him.

Sir CHARLTON BRISCOE, Bt., M.D., F.R.C.P.

Sir Charlton Briscoe, consulting physician to King's College Hospital, died at his home in Suffolk on February 28. He was 85.

John Charlton Briscoe was born on April 8, 1874, the second son of a business man, Sir John James Briscoe, first baronet, and sometime High Sheriff of Cambridgeshire. Charlton Briscoe was educated at Harrow and King's College, which he entered with a Warneford Scholarship. In the next few years he gained many prizes both at King's College and King's College Hospital, and in 1896 he was prosector at the Royal College of Surgeons. Qualifying in 1898, he graduated M.B. in 1901, took the M.R.C.P. in 1902, and proceeded M.D. in 1903. After holding the post of house-physician to Sir David Ferrier—at that time, he said, the competition for resident posts at King's was negligible—he became Sambrooke medical registrar. In his student days he was a notable games player, representing his hospital at rugby and association football and at cricket.

After a period of study at Göttingen under Professor Aschoff, he returned to King's College Hospital as senior medical tutor and registrar, and in 1908 he was appointed assistant physician. From 1910 to 1911 he was dean of the medical school, in 1915 he was promoted to physician, eventually becoming senior physician. Other hospitals to which he was attached were the Evelina Hospital for Sick Children and the St. John and Elizabeth Hospital.

During the first world war he was gazetted major, R.A.M.C., and in 1918 he became vice-president of the Ministry of Pensions special medical board for shell-shock. He gave the Arris and Gale lecture at the Royal College of Surgeons in 1919 on the mechanism of post-operative collapse of the lungs. At the Royal College of Physicians he was elected F.R.C.P. in 1910, became a member of council in 1929, and he was senior censor from 1933 to 1934. He was Lumleian lecturer in 1927, his subject being the muscular mechanism of respiration and its disorders. At both the College and at the Society of Apothecaries of London he was an examiner in medicine.

His main interest was in respiratory disease, and he wrote many papers on the subject, one on the treatment of pulmonary disease by vaccine appearing in this journal in 1909. Several of the popular textbooks of his day contained articles from his pen. He was president of the Section of Medicine at the Royal Society of Medicine from 1935 to 1937.

Sir Charlton succeeded to the title in 1921, when his elder brother died. His family seat was at Lakenheath Hall in Suffolk, where he took a great interest in farming. In later life shooting was one of his favourite recreations. Only two years ago he gave an entertaining talk to the Listerian Society at King's College Hospital; but he found the surroundings there unpropitious for reminiscence. "I prefer," he said, "six inches of snow, an eight-mile walk, a bath before dinner, and then to sit around a big open-hearth wood fire in half light with a dish of walnuts and, most important of all, a decanter of port."

Sir Charlton Briscoe married Dr. Grace Maud Stagg in 1909. She survives him with two sons of the marriage.

FRANK BARNES, LL.D., M.S., F.R.C.S.

Mr. Frank Barnes, formerly honorary surgeon to the General Hospital, Birmingham, lecturer in anatomy and in operative surgery in the University of Birmingham, died at the Queen Elizabeth Hospital on February 18 in his 91st year.

Frank Barnes, born in Birmingham in 1869, the son of Mr. and Mrs. Joshua Barnes, was trained at Borough Road Training College for the profession of school-teaching. The quiet determination with which a penniless schoolmaster without the aid of any significant scholarship award trudged the difficult route of medical training to become one of Birmingham's most notable surgeons has always been a source of excitement and admiration to his many friends. From Mason College and the University of Birmingham he qualified in 1898 and graduated M.B., B.S. London four years later. Determined to pursue a surgical career, he obtained the Fellowship of the Royal College of Surgeons of England in 1902, and achieved the Mastership of Surgery in the University of London in 1903, the year in which the first great ambition of his life was fulfilled, his election to the staff of the General Hospital as honorary assistant surgeon. He had progressed to this through several resident appointments at his own hospital, at the Children's Hospital, Birmingham, and at the Royal Northern Hospital in London. During the first world war he served as a captain in the R.A.M.C. In 1917 he became a senior honorary surgeon to the General Hospital, serving till 1929, when at the retiring age of 60 he was made consulting surgeon. In this active stage of his surgical life he was also consulting surgeon to the Birmingham and Midlands Eye Hospital, the Sutton Coldfield Cottage Hospital, and the Hospital of St. Cross, Rugby. His main activity, however, apart from his devoted surgical service to the General Hospital, was as surgeon to the Birmingham Orthopaedic Hospital (now the Royal Orthopaedic Hospital).

[Birmingham Post and Mail

In the medical life of Birmingham he took a very prominent part in his day, being a past-president of the Birmingham Branch of the B.M.A. and of the Midland Medical Society. In 1957 the University of Birmingham conferred on him the honorary degree of Doctor of Laws, and at the degree-giving ceremony the Public Orator said:

"It is with surgeons as with friends: when we part we leave something of ourselves with them. Doubly is that so if our surgeon is our friend; and a host of grateful patients who recovered their health through his [Frank Barnes's] kindly ministrations have awakened to the feeling that he had given them more than he took from them."

Professor A. L. D'ABREU writes: Frank Barnes achieved a reputation that will stand the test of time on two counts. Entering surgery at a time of evolution when the audacity of Lawson Tait allied to the then-established principles of Listerism had opened the way, he had the ability and confidence to develop a steadily increasing repertory of surgical procedures. All who saw Barnes (and the writer

had the privilege of being his surgical dresser) speak of his superb technique and masterful dexterity; he was always an admirer of the gentle surgery and careful haemostasis advocated by Halsted and Moynihan. Not content with mastering the operations of the day within the abdomen, he extended his endeavours into the neurosurgical and orthopaedic fields, being probably the first in the Midlands to operate on the Gasserian ganglion and the spinal cord. He taught by example, being too shy and unassuming to be an eloquent speaker at the bedside or in the lecture room; his care in history-taking and in physical examination made him the safest and wisest of diagnosticians. Any of his former house-surgeons would agree with this estimate. He developed a large surgical practice and was one of the most successful surgeons of his era; even at the age of 90 he was remembered by many as a master surgeon and always delighted to talk of surgery.

The second pillar on which his reputation will survive is his thoughtful and great generosity to his own medical school and university. In this he showed the enthusiasm and loyalty of his great friend, Dr. Stanley Barnes, during whose deanship the new medical school and the Queen Elizabeth Hospital at Edgbaston were opened. Frank not only founded the Barnes postgraduate surgical travelling fellowship but gave munificently to the Queen Elizabeth Hospital and to the new medical school library which shares his name with that of Stanley Barnes. The name "Barnes" over the entrance to this great library will perpetuate the memory of two great students of the Birmingham School.

Generous and friendly by nature, he shared his friendship with many; he liked to live well and to share his delights in food, wine, and cheese with others. A great fisherman by any standards, his modesty in this and all things never allowed him the exaggerations commonly attributed to anglers. His knowledge of flowering shrubs was great, as could be seen on the most cursory visit to his home at King's Norton.

Many lay and medical friends in the Midlands mourn the loss of this great man whose faculties remained keen and alert to within a few days of his death. He ended a rich, full, and happy life which has greatly furthered the progress of surgery and of his medical school, in the quiet unostentatious way in which he had lived it.

D. B. writes: All who had the privilege of knowing Frank Barnes will remember him as a man of outstanding ability, a gifted surgeon, and a very generous friend to the medical school of Birmingham University. I have lasting memories of numerous visits to his house, wherein he was such a delightful host, and being taken all over his garden and greenhouses; he would tell you the names of every shrub, flower, and plant, his real love being in cultivating perpetual flowering carnations, which he so generously gave to his guests.

My late husband was a very close friend of Frank Barnes, and almost every Sunday morning they met and had numerous conversations on many subjects, especially medical matters and how much things in the medical world had changed for the better or the worse (who knows?) since 1898. I well remember Frank Barnes telling me of the night he was called out to attend my mother-in-law at the remote village of Drayton, Nottingham, and upon his arrival he decided he must operate at once: this he did on the kitchen table (still in the family of my late husband), and she is still well and alive to-day at the age of 87.

Frank Barnes worked hard, very hard, but always found time to enjoy his well-earned leisure, golfing, fishing, reading, love of classical music, and period furniture, china, and silver. There must be many of his friends who have some happy recollections of his charming self, and in view of the wonderful library he has given to the University in conjunction with his namesake, the late Stanley Barnes, I feel that some sort of biography of the lives of both these eminent Birmingham men should be written for the benefit of future students.

A. C. AINSLEY, *M.C.*, M.B., F.R.C.S.

Dr. A. C. Ainsley, honorary consulting surgeon to the Hartlepools group of hospitals, died in hospital on February 16.

Born seventy years ago in Hartlepool, Alan Colpitts Ainsley was the second son of a well-known general-practitioner surgeon, Dr. T. G. Ainsley. He received his early education at Malvern College and his medical training at Caius College, Cambridge, and the London Hospital, qualifying in 1915. He served in the R.A.M.C. in the Near East in the first world war, gaining the Military Cross. On demobilization he studied for and, in 1922, obtained the F.R.C.S. of England.

Refusing to practise as a specialist in surgery, he joined his father in general practice, and on the retirement of the latter carried on the practice with his uncle, the late Dr. MacGill. At the end of the second world war he joined his brother-in-law, Dr. J. E. Mitchell, but retired on account of bad health in 1957. He held several appointments in the Hartlepools. Shortly after his return to civil life he was appointed honorary surgeon to the Cameron Hospital, a post which he held with distinction. Later he became medical superintendent of the Public Assistance Hospital, later to become the General Hospital. For a short time he was orthopaedic surgeon to the Hartlepools Hospital. On the advent of the National Health Service he was appointed surgical consultant to the group of hospitals. Chairman of the Hartlepools Division of the B.M.A. in 1933–4, he was president of the Teeside Branch in 1954.

A colleague writes: Dr. Ainsley's death has removed a loved and respected figure in medical circles. He sought no personal advantage, and his kindness to patients in and out of hospital earned him the love and esteem of those whom he had under his care. He was a gifted surgeon of sound judgment whose technique was admired by his colleagues. Until a few years before his death he enjoyed his game of golf, but his annual holiday fishing on a Scottish loch was to him the most enjoyable form of relaxation, especially when accompanied by his charming wife, also a doctor. One cannot close this short note without mentioning his great love of animals. He detested the slaughter of animals in the name of sport, and was often very outspoken about this and the use of animals in laboratory experiments. His final illness was borne with great courage, as he knew the inevitable result. To the writer he expressed his tiredness as the disease progressed, and it might be said of him, as Walter Savage Landor wrote,

> I warmed both hands before the fire of life;
> It sinks, and I am ready to depart.

W. P. MACCALLUM, C.B.E., D.S.O., *M.C.*, M.B. Ch.M., F.R.A.C.P.

Dr. W. P. MacCallum, honorary consulting physician to the Royal Prince Alfred Hospital, Sydney, and formerly honorary treasurer of the Royal Australasian College of Physicians, died in Sydney on November 22, 1959.

Walter Paton MacCallum was a son of the late Professor Sir Mungo MacCallum, K.C.M.G. Having fought in the first world war he returned to Australia to study medicine at the University of Sydney, where he graduated in 1924. After holding the post of resident medical officer at the Royal Prince Alfred Hospital and other resident appointments he was appointed to the honorary staff of the Royal Alexandra Hospital for Children in 1926 and to the Royal Prince Alfred Hospital in 1934.

He became a Member of the Royal Australasian College of Physicians in 1939 and was elected a Fellow in 1946. Meanwhile he had served with great distinction during the second world war in the Australian Army Medical Corps.

From 1948 to 1950 he was honorary secretary of the College and from 1950–58 honorary treasurer. He was also for a period of four years Honorary Physician to the Governor General.

N. H. F. writes: Walter MacCallum was a brilliant combatant and staff officer in the first world war when he served in Egypt and France, being awarded both the D.S.O. and *M.C.* and was three times mentioned in dispatches. Efforts were made to retain his services permanently in the Army, but he decided to take up medicine as his future career and did so very successfully.

In the second world war he was on active service in the Middle East, Greece, Crete, Netherlands East Indies, and the South-West Pacific Area. He ultimately became Deputy Director General of Medical Services, A.M.F., was mentioned in dispatches and appointed C.B.E. I first met him in the Middle East during the war and have been closely associated with him since that time. His integrity, singleness of purpose, and devotion to duty were outstanding characteristics; with his abundant energy and vitality he never spared himself in the service of others. He was a good diagnostician and teacher, and was always full of consideration for patients under his care.

When we were in the Netherlands East Indies, one incident illustrating his great courage may be cited. Hearing that a group of soldiers in the Allied Forces were in a precarious position and having difficulty in extricating themselves, MacCallum disappeared, returning safely with them some days later. Needless to say he discarded all evidence of his association with the Australian Medical Corps when so doing, but had he fallen into Japanese hands his fate would have been disastrous.

MacCallum was a delightful friend and colleague, and his home life and background reflected his great charm. His sudden death came as a great shock to all who knew him. He was a devoted husband and father, and to his wife and family we extend our deep sympathy in their great bereavement.

T. D. PRATT, M.R.C.S., L.R.C.P.

Dr. T. D. Pratt, who recently retired from practice at Wortley, Leeds, died at his home near Thirsk on January 18. He was 66 years of age.

Thomas Dawson Pratt was born in Bradford and educated at Bradford Grammar School and Leeds University, for which he played rugby football. He was in the O.T.C., and at the beginning of the first world war he was commisioned in the Duke of Wellington's Regiment, and went to France with the British Expeditionary Force in 1915. He was severely wounded, and later resumed his interrupted studies, qualifying in 1918. He entered general practice in Lower Wortley, and continued there until his last illness.

He rejoined the Territorial Army before the second world war as registrar of the 18th General Hospital, and was mobilized at the outbreak of war. He went out to Egypt with his unit, and after the other officers had been posted to Malta he assumed command. Later he took the unit to India, where he served with efficiency and distinction. He returned to the United Kingdom on the news of his wife's illness, but was not able to arrive back before her lamentable death.

Dr. Pratt gave good service to his fellow practitioners. He was a member of the Leeds executive council and the Leeds medical committee, serving on both for many years. In committee he brought valuable opinions and judgments from his long experience. He was editor of the "Bulletin" of the Leeds medical committee, and gave good and balanced accounts of its work. He also published a "History of the 18th General Hospital," which gives a full and interesting account of his old unit. After the war this became the 18th C.C.S., which he commanded with distinction for three years.

He was a devoted family man, and had a kind and most amiable disposition. He was ever at the disposal of the many patients in his practice, who were extremely fond of him. On his retirement in 1958 he was given many tokens of gratitude for his long and ungrudging labours in his beloved Wortley. A keen Christian, Dr. Pratt was one of the patrons of St. John's, and at the memorial service there was a large congregation of mourners. He was interested in most of the social events, and the Pratt family will be long remembered for their influence for good.

He leaves a son, Dr. T. L. C. Pratt, who is consultant radiologist at Darlington, and a very devoted daughter, Pat, who was theatre sister at Leeds General Infirmary, and to them our deepest sympathy is extended.—J. E. R.

A. P. B. writes: The medical profession has lost a gallant member in the death of Thomas Dawson Pratt. "T. D.," as he was known to his many friends, was retained in England after recovery from his wounds in 1916 to continue his studies at the Leeds medical school. He acted as unqualified houseman—both physician and surgeon—at the General Infirmary at Leeds and later as resident medical officer at the public dispensary in the same city in company with A. A. Roberts and myself. Though he had the ability he cared nothing for the limelight of specializing, his object being to become the ideal G.P. In this he was singularly successful, earning not only his living but the love of his many patients. He remained in practice in Wortley for 38 years. He was popular in the best sense of the word. Three years ago he had the first symptoms of heart disease, and on the eve of his retirement to Thirsk he had a second coronary thrombosis, from which he never really recovered.

P. WOOD, M.R.C.S., L.R.C.P.

Dr. P. Wood, who practised first in Crawley and later in Welwyn Garden City, died on November 12, 1959, aged 87.

Percival Wood, the son of the Rev. Robert Wood, was born on August 7, 1872, at Erith, Kent. Educated at Marlborough College, Cambridge University, and St. Bartholomew's Hospital, he qualified in 1897. He served as a civilian surgeon in the South African Field Force during the war in South Africa and during the first world war he was a Captain in the R.A.M.C. He had a large and successful practice in Crawley, Sussex, and in 1932 moved to Welwyn Garden City, where he remained in practice until he retired in 1946.

J. S. R. writes: Dr. Wood was a highly respected and kindly practitioner and I was indeed fortunate to start in general practice under his wise guidance. Despite his practice commitments he found time to give his services to public work. He was chairman of Crawley Cottage Hospital and later of Welwyn Garden City Cottage Hospital, where he was tireless in his endeavours to obtain the permission of the Ministry for rebuilding and modernization. He was a justice of the peace, serving on the bench at Horsham, and for three years he was a member of the Welwyn Garden City urban district council. Both at Crawley and later at St. Francis, Welwyn Garden City, he was a church worker.

One of his great loves was music. As a boy he was frequently an invited soloist at St. Paul's Cathedral and he grew into a fine bass singer. He died two years after his wife, who shared his enjoyment in music, and he is survived by one son and four daughters, two of whom are professional musicians.

Sir ROBERT HUTCHISON, Bt., M.D., LL.D.
F.R.C.P., Hon.F.R.C.P.Ed.

The obituary of Sir Robert Hutchison was published in the *Journal* of February 20 (p. 571).

Dr. S. LEONARD SIMPSON writes: Having served under Sir Robert Hutchison for three years, as his registrar and first assistant, I learnt to appreciate the greatness and warm kindness of his austere personality. His teaching was fundamental, direct, and essentially simple; his intellect

penetrating and his logic impeccable; his clinical judgment and the decisiveness of his opinions were remarkable, and his ward rounds brought a sense of resolution and security to patients, students, housemen, and nursing staff alike.

He was contemptuous of verbosity and pomposity and of niggardly controversy, which he ignored like many other things not worthy of his attention. Commencing as a physiologist, he had a worthy regard for scientific research and modern investigation, but not when applied in blunderbuss fashion or devoid of clinical judgment. Those who were privileged to enjoy his friendship realized the kindness and sympathetic understanding which his reticence usually obscured. He was undoubtedly an intellectual giant in his generation, and both the man and his teachings will be remembered for all time.

Medical Notes in Parliament

NEW HOSPITAL BUILDING LIST

The MINISTER OF HEALTH announced in answer to a question by Lord BALNIEL (Hertford, Con.) on February 29 that he had asked hospital boards to bring to completion the planning of a number of additional major projects.

These include (he stated) work on a number of new hospitals. There is the first phase of a new teaching hospital in Liverpool, a new maternity hospital to replace the Birmingham Maternity Hospital, and a new building for the Tavistock Clinic. There are further stages of the new general hospitals for Crawley and Truro, and the completion of those for Harlow and Huddersfield and of the mental deficiency hospital at Oakwood Park, Conway. The list also includes the first phase of the redevelopment of the Gloucestershire Royal Hospital and a further stage of the development of the Poole General Hospital.

New maternity departments are proposed at the Norfolk and Norwich Hospital, Ashton-under-Lyne General Hospital, Burnley General Hospital, Chester City Hospital, Margate General Hospital, and Watford. An obstetric unit will form part of a large development at the New Cross Hospital and Royal Hospital at Wolverhampton, and there will be a new out-patient department at Queen Charlotte's Hospital. There will be a new ophthalmic block at the Royal Berkshire Hospital, Reading, and a neurosurgical unit at Walton Hospital to serve the Liverpool hospital region.

Large developments proposed at other hospitals include a surgical block at Derby City Hospital, an operating-theatre suite and diagnostic radiology department at the Prince of Wales's Hospital, Tottenham, a new out-patient department for St. John's Hospital, Battersea, and extensions to the Southend General Hospital. There will be a new ward block at the Christie Hospital, Manchester, extensions to the Scalebor Park Mental Hospital at Burley-in-Wharfedale, and improvements to St. George's Mental Hospital, Morpeth. The engineering services at St. John's Hospital, Stone, are to be modernized, and new boilers and a laundry are included for the Newcastle General Hospital.

HEALTH SERVICE SPECTACLES

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The Commons have partly revived a pre-war practice to give back-bench M.P.s more occasions to introduce topics for debate. There is in this experiment, which began on February 22, opportunity for only one debate instead of the former two; and it did not have a noticeably auspicious start, since Commander H. PURSEY (Hull, East, Lab.), who won first place in the ballot, and used the occasion for a grand offensive in a campaign he has been pursuing for some time, himself occupied more than an hour of the available three.

Commander Pursey's Allegations

Commander PURSEY is worried about the sale of Health Service spectacles—or, as he would put it, the neglect of Health Service frames in favour of high-pressure salesmanship to impose on uninformed patients the purchase of private frames at considerably higher prices. His motion, while recognizing the success of the Supplementary Ophthalmic Service, complained of the failure of some opticians to offer the complete service available under the National Health Act, and called on the Government to see that this was remedied. The essence of his case, which he illustrated with accounts of personal visits to various opticians in London and the suburbs and in Hull, was that the Service frames are hidden away in drawers instead of being on display for patients to see, and that when a sufficiently strong demand is made they are produced with derogatory if not derisory comments implying that they are of little value and nobody asks for them. He alleged that there was a failure to provide a full short-notice emergency service for breakages; that the full range of colours available for N.H.S. frames was not shown; and that the official notice setting out the scale of fees and charges was not adequately displayed.

"An Immoral Professional Association"

Part of this attack was directed specifically at "these false medical eye centres"—the "plumber's shop," as he described it, of the dispensing optician for frames, with a room for a doctor for occasional sight tests. The firm engaged the doctors, and provided the staff as well as the accommodation for the doctors to attend when they were called. The B.M.A. Ethics Committee of a previous generation would turn in their graves, he felt sure, if they knew that doctors were being employed by "plumbers" and called by telephone in the same way as a taxi or a district nurse. This "racket" was an immoral professional association between doctors and tradesmen arranged by the big optical firms with the B.M.A. before the Health Service came into operation. The object was obvious—to squeeze out the "pukka optician" (his term for the ophthalmic optician, in contrast to the "plumber") and get all the sight-testing into the hands of doctors and the dispensing into the plumbers' shops. The title "medical eye centre" was false and misleading, since nothing medical was done there; doctors tested sight, but did no eye health work there.

Facts of the Case

Mr. RONALD RUSSELL (Wembley, South, Con.), who sponsored the Opticians Act, 1958, produced to counter these allegations the facts that in the 12 years of the Supplementary Ophthalmic Service more than 50 million people had had their eyes examined, 80% of them by ophthalmic opticians and 20% by ophthalmic medical practitioners. Stringent terms of service were laid down for both in the N.H.S. (Supplementary Ophthalmic Service) Regulations, 1956. There was a high ethical standard among all three participants in the Service—medical practitioners, ophthalmic opticians, and dispensing opticians. There had been fewer recorded complaints against them than against any other part of the Health Service. The notice that Commander Pursey had claimed was not shown was usually displayed in an optician's consulting-room or waiting-room, but possibly not in a shop.

Miss EDITH PITT, Parliamentary Secretary, Ministry of Health, endorsed this, stating that none of the allegations made from time to time by Commander Pursey had been referred to a Health Service executive council. Cases needing investigation were few, about 25 a year. The form

sent to every member of the public using the service stated that a full range of frames was available, and a duty was laid on opticians to make the public aware of what was available to them. Most opticians were believed to display the Ministry of Health notice, or notices provided by their own associations.

Notice Being Displayed

An examination had taken place in four areas as a result of questions asked by Commander Pursey. In south-west London 81 out of 131 premises visited displayed the notice, and the remaining 50 willingly accepted another copy for display; in Putney, four out of five; in Middlesex and Surrey informal inquiries through the executive council confirmed that most opticians displayed the notice. One firm mentioned by Commander Pursey during his speech had asked for extra copies, and there had been a demand from other firms. To make the display of the notice compulsory would require an amendment to the terms of service, and would be out of keeping with the professional status of opticians. Notices explaining dental and prescription charges were not compulsory.

"Medical Eye Centres"

"Medical Eye Centres" was a term used by the Ophthalmic Treatment Board Association, and was not part of the official terminology in the Ministry, but its use involved no breach of the terms of service. It was part of the former National Health Insurance, and a high proportion of ophthalmic medical practitioners worked at these centres. The patient was free to take the prescription anywhere he liked for dispensing. The critical part of the motion was unwarrantably wide in its scope; the call to ensure that the full service was made available was met with an assurance that the Government were prepared, in consultation with the profession, to explore what could be done to improve the supply of information to the public, including the range of spectacles obtainable through the Health Service.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) first took her severely to task for the reluctance to compel opticians to display the notice; and then offered the suggestion that ophthalmologists and opticians should be closely associated with industrial health centres, and the opinion that the final objective should be a salaried service for opticians working in health centres. She added a plea that fashion trends in frames should be incorporated in Health Service models.

QUESTIONS IN THE COMMONS

Abuse of Domiciliary Consultations

Sir GODFREY NICHOLSON (Farnham, Con.) asked the Minister of Health on February 29 if he would summarize the replies he had received from regional boards in answer to his request of February, 1959, that they should give him the factual information on which he could base a decision whether to institute an inquiry into the operation of the domiciliary consultative service; and how this information compared with the evidence from hospital authorities reported by the Select Committee on Estimates of 1956–7; and what decisions he had taken on the recommendations made by the Select Committee on Estimates of last session regarding an inquiry into the operation of the domiciliary consultative service; and what form that inquiry would take.

Mr. D. WALKER-SMITH said that replies from boards revealed little information indicating abuse of the service, and in such rare or doubtful cases as transpired action was taken with a view to putting it right. The replies also revealed the difficulty of obtaining factual information of any abuse in present circumstances. As this aspect of the consultant services among others was before the Royal Commission on Doctors' and Dentists' Remuneration, he decided to await their report before proceeding; and now that the report had been received he would consider what action was appropriate in this as in other respects.

Sir GODFREY NICHOLSON said that when the Minister agreed to an inquiry he sought the facts from the people who were criticized, and not until the matter was reopened by the Select Committee did he agree to seek the facts from the regional boards. Did the evidence he received contradict that given to the Select Committee, and why was there this continued delay in answering what was a rather serious charge by the Select Committee? Mr. WALKER-SMITH said the replies from the regional boards were collated in June last year. In effect, they were summarized in what he had said—they revealed little information to show any abuses in the service. Any individual cases which did so had been followed up. He would consider whether it was possible to get any further and fuller information.

Dr. EDITH SUMMERSKILL said the recommendations of the Select Committee could not be reconciled with those of the Royal Commission on Doctors' Remuneration. Could the Minister say to which group he attached most importance? Mr. WALKER-SMITH replied that the judgment of Paris paled in comparison with the difficulty of the choice put to him. He viewed with great respect both the recommendations of the Royal Commission and the observations of the Select Committee. He did not think there was necessarily any contradiction. What the Royal Commission had done was to make no recommendation on the specific control of this service, but said that no change should be made in the circumstances in which payment should be made.

Congenital Abnormalities

Mr. SYDNEY IRVING (Dartford, Lab.) asked the Minister, as representing the Minister for Science, what reports he had had made to him recently on progress in the understanding of chromosome behaviour in relation to human abnormalities. Mr. WALKER-SMITH replied that he was glad to be able to report that substantial progress had been, and was being, made in the understanding of chromosome behaviour in relation to human abnormalities. A number of reports on new knowledge in this field had been published in the scientific literature.

Mr. IRVING asked if this was a first step which would some day lead to the prevention of mongol births. Mr. WALKER-SMITH told him that this relatively new technique was advancing the understanding of the causation of mongolism, and the next step was no doubt its prevention. Dr. EDITH SUMMERSKILL asked if he would consider keeping a comprehensive list of congenital abnormalities. Mr. WALKER-SMITH said that anything that would facilitate research would be considered by the Medical Research Council and the Minister for Science.

Habit-forming Drugs

Mr. FRANCIS NOEL-BAKER (Swindon, Lab.) asked the Minister whether, in view of the increasing number of habit-forming drugs advertised and on sale to the public without prescription, he would make it obligatory on manufacturers of such products to print a full declaration of their contents, in terms comprehensible to the layman, not only on the container as at present, but also on the wrapper or box and on all advertisements and literature relating to such products; and also whether, in view of the dangerous substances contained in such products, he would seek power to extend to all products appertaining to health on sale to the general public the regulations governing the declaration of contents of proprietary medicines and drugs. Mr. WALKER-SMITH told him that these suggestions would require new legislation and that he would arrange for them to be examined in the review of legislation relating to the control of medicinal substances now being undertaken.

Convalescent Information Bureau

Mr. L. PAVITT (Willesden, West, Lab.) asked if the Minister would establish a convalescent information bureau to advise on the placing of patients needing convalescent

treatment. Miss EDITH PITT, Parliamentary Secretary, said that the proposal to establish a bureau of this kind for the London hospital regions was to be discussed with the regional boards concerned on March 17.

Arsenic in Potatoes

Mr. JOHN EDEN (Bournemouth West, Con.) asked the Minister of Agriculture, Fisheries, and Food what evidence he had received regarding the presence of dangerous amounts of arsenic in the peel of potatoes which have been treated with arsenical haulm killers. Mr. J. HARE stated on February 25 that, where arsenic was found in potatoes, the peel normally contained more arsenic than the flesh; but surveys organized by the Ministry of Health in 1958 and analysis of samples of tubers from sprayed crops taken by the National Agricultural Advisory Service in 1959 had indicated that the residues would not be dangerous to public health. Moreover, there were stringent statutory limits to the amount of arsenic which might be in any food, including home-grown and imported potatoes as sold.

Finding a Locum Tenens.—Mr. L. PAVITT asks us to print the following correction of what he said in the House of Commons on February 22 (*Journal*, February 27, p. 658). In his supplementary question on locums he states he said: "In view of the fact that so many of these difficulties occur because of the failure to solve these problems at the local level, will the Minister give consideration to the introduction of a scheme for a national locum service? And further, will he consider the possibility of using the trainee assistants scheme in order to help in this respect? For example, if the trainee were given two months at the end of the normal training to do locums and enable him to obtain wider experience in general practice and also in hospitals, that would help. Will he also consider the possibility of short refresher courses for consultants and specialists, so that they may come down into the arena of family doctoring, which might be beneficial to them and help the general practitioner in solving his problem of locums?"

Universities and Colleges

UNIVERSITY OF LONDON

Mr. Kenneth McLay, Leverhulme Research Fellow at the Institute of Laryngology and Otology, has been appointed to the University Readership in Otology tenable at that institute.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on February 2, with the President, Dr. A. Rae Gilchrist, in the chair, the following were elected Members of the College:

A. L. K. Rankin, R. S. Hoon, I. S. Trotter, B. D. Dharmasena, M. H. Zafar, K. D. Coorey, Mary Cherian, R. S. Wells, S. J. Surtees, G. P. Lewis, D. J. Woods, W. A. G. Roper, R. Singh, S. K. Mitra, B. G. S. Murthy, C. Protheroe, J. C. Maclaurin, P. K. Basu, K. M. Cherian, T. Ohn, N. H. Rizavi, K. K. Sinha, R. K. Seth, M. H. Yee, Kathleen A. Irvine, G. W. Fenton, F. Moran, N. A. Jadhav, Freda M. Paul, I. Sh'A. Audu, C. K. Ramachandran, Y. C. Wong, J. S. Fleming, V. Thuraisingham, F. P. Retief, J. G. Richards, M. Sarkar, L. L. Wilson, K. V. S. K. Das, U. B. Rao, F. Po-Tun Fok, W. E. Ince, I. T. Draper, S. Louis, E. S. Paykel, A. D. Gupta, D. F. Scott.

UNIVERSITY OF DUBLIN

SCHOOL OF PHYSIC, TRINITY COLLEGE

R. P. Brown has been approved at the examination for the degree of M.D.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

At a meeting of the Faculty on February 1, with the President, Mr. Arthur Jacobs, in the chair, the following were admitted Fellows of Faculty: *qua* Physician, P. K. Ramaswami; *qua* Surgeon, R. L. Agarwal, A. D. George.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At a meeting of the College, held on February 5, with the President, Dr. P. T. O'Farrell, in the chair, the following were admitted to the Licence and Membership of the College: R. Carroll, D. C. Curtin, J. P. Duffy, J. S. Wright.

Vital Statistics

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available

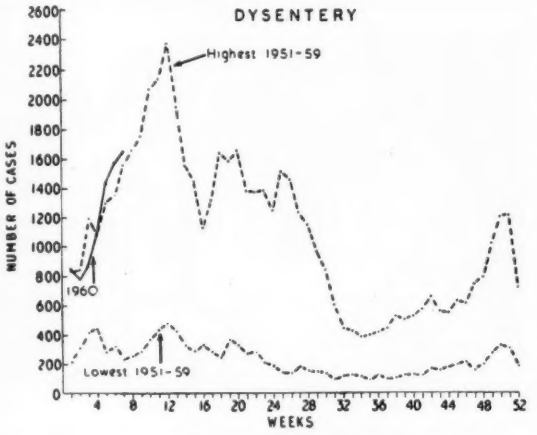
	Week Ending Feb. 13	Week Ending Feb. 20
Measles		
Kent	108	**150**
Ashford U.D.	8	**71**
Dover M.B.	55	**60**
Devonshire	148	**224**
Exeter C.B.	88	**165**
Gloucestershire	88	**155**
Cheltenham M.B.	26	**89**
Lancashire	358	**408**
Blackpool C.B.	72	**58**
Liverpool C.B.	66	**141**
Dysentery		
Dorsetshire	22	**19**
Portland U.D.	18	**16**
Essex	78	**101**
Dagenham M.B.	1	**14**
Maldon M.B.	5	**11**
Romford M.B.	8	**21**
Saffron Walden M.B.	35	**26**
Kent	48	**49**
Deal M.B.	36	**21**
Margate M.B.	0	**11**
Lancashire	413	**459**
Bolton C.B.	30	**26**
Liverpool C.B.	48	**54**
Oldham C.B.	50	**80**
Preston C.B.	38	**28**
Ashton-under-Lyne M.B.	33	**64**
Leigh M.B.	13	**16**
Swinton and Pendlebury M.B.	43	**48**
Lincolnshire	33	**32**
Louth M.B.	10	**16**
London	220	**200**
Camberwell	15	**16**
Greenwich	3	**16**
Islington	26	**32**
Southwark	48	**25**
Wandsworth	16	**21**
Nottinghamshire	19	**36**
Barford R.D.	7	**11**
Newark R.D.	2	**13**
Wiltshire	24	**75**
Swindon M.B.	2	**40**
Yorkshire North Riding	20	**26**
Redcar M.B.	17	**20**
Yorkshire West Riding	93	**130**
Bradford C.B.	25	**31**
Sheffield C.B.	20	**38**
Monmouthshire	7	**25**
Monmouth M.B.	0	**14**
Nantyglo and Blaina U.D.	0	**10**
Diphtheria		
Warwickshire	0	**2**
Birmingham C.B.	0	**2**
Acute Poliomyelitis		
Leicestershire	1	**3**
Barrow upon Soar R.D.	1	**2**

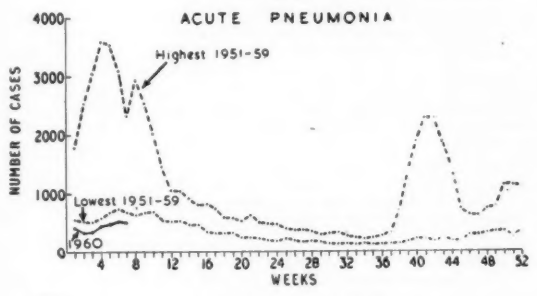
Influenza in England and Wales

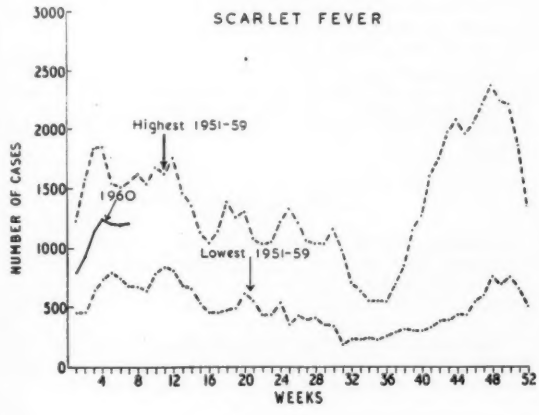
The deaths from pneumonia (716), bronchitis (760), and influenza (42) were all rather higher during the week ending February 20 than during the preceding week. On the other hand, they were very many fewer than in the corresponding week last year. Influenza virus A or B has not so far been isolated from cases of illness this year, and there is no evidence from the laboratories that influenza is prevalent. The number of applications made to the Emergency Bed Service in London remained about the same, at 1,270.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 13** (No. 6) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	6	0	0	0	4	5	0	4	0	2
Dysentery	1,578	220	305	13	6	1,346	88	97	37	7
Encephalitis, acute	5	0		0		3	0		0	
Enteric fever:										
Typhoid	4	2	0	0		2	0	1	0	
Paratyphoid	1	0	0	0		3	1	2(B)	0	
Food-poisoning			4	0		125	18	9	0	
Infective enteritis or diarrhoea under 2 years				4	18				12	21
Measles*	1,541	34	11	7	20	25,157	1400	594	405	1007
Meningococcal infection	13	0	5	2	1	30	5	9	0	1
Ophthalmia neonatorum	22	0	4	0		24	1	7	0	
Pneumonia†	505	35	270	9	2	1,465	142	663	16	14
Poliomyelitis, acute:										
Paralytic	4	1	0	1	1	11	1	0	0	
Non-paralytic	1	0	1			0	0	2		
Puerperal fever§	179	22	11	1	0	237	40	10	0	1
Scarlet fever	1,192	49	85	31	23	1,218	60	64	27	29
Tuberculosis:										
Respiratory	446	46	67	7		457	55	75	15	
Non-respiratory	497	6	12	2		50	1	14	3	
Whooping-cough	987	85	230	9	23	788	26	54	90	140

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		3	0		0	
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	7	0	1	0	0	12	0	1	2	0
Influenza	38	0	3	0	2	455	44	29	1	0
Measles	1,541	0	0	0	0		0	1	0	0
Meningococcal infection		0	0				1	1		
Pneumonia	657	45	28	16	5	1,373	177	117	30	16
Poliomyelitis, acute	1	0		1	0	0	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	80	2	10	0	5	108	9	14	0	2
Non-respiratory		3	1	0	0		2	0	0	1
Whooping-cough	2	0	0	0	0	4	0	0	0	0
Deaths 0–1 year	333	43	28	7	18	405	45	43	14	16
Deaths (excluding stillbirths)	11,039	915	639	131	182	15,007	1509	1146	169	228
LIVE BIRTHS	14,426	1318	997	252	369	14,592	1243	1092	254	403
STILLBIRTHS	277	19	22			310	20	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia

Medical News

Royal Society Tercentenary Celebrations

Sir CYRIL HINSHELWOOD, P.R.S., has given details of the Royal Society's tercentenary celebrations, which will take place between July 18 and 26.

These will include 10 Tercentenary lectures by Fellows, exhibits to illustrate important aspects of research, and visits to laboratories and research centres. Oxford, Cambridge, and London Universities will be holding honorary degree ceremonies, and invitations to the general celebrations have been sent to representatives of national academies and universities in 44 countries.

Colonial Development and Welfare

In 1958 to 1959 the Colonial Research Council spent £789,974 on research schemes, states the report *Colonial Research, 1958–9* (H.M.S.O., price 18s.).

Medical research accounts for 17% of the allocation for research—the second largest allocation. Projects started during the year included research on tropical virology at the London School of Hygiene and Tropical Medicine (£1,750); studies in folic acid metabolism at Birmingham University (£2,100); research on bilharzia by the Medical Research Council (£4,580) and on the toxaemia of pregnancy at the University of Hong Kong (£3,667); and a study of factors influencing arterial blood pressure in Jamaica (£4,874).

Medical Art Society Exhibition

There is something peculiarly piquant about what cobblers produce when they abandon their last, and many people will go to see the Medical Art Society's 18th exhibition at the Walker Galleries, 118, New Bond Street, more for the sake of the profession than for the sake of art. The doctor, on the whole, is a Sunday painter—well in the traditions of Sir Winston Churchill and Grandma Moses—who produces colourful pictures, mainly traditional in style and easy to view. Many of the 148 paintings, watercolours, and drawings deal with holiday places; there are a few portraits, a mere handful of abstracts, and seven pieces of sculpture. The secretary of the society is Dr. A. M. RACKOW, Fourways, Windy Ridge Close, Wimbledon, London, S.W.19. The exhibition is open daily from 10 a.m. till 5 p.m., Saturdays 1 p.m., and closes on March 17.

Additions to B.M.A. Film Library

Copies of the following films have been presented to the film library by British Insulin Manufacturers Association, Vauxhall Motors, Ltd., and William R. Warner and Co. Ltd.:

A Talk About Insulin. 16 mm. Sound. Colour. 17 min. 1959. Made by Film Surveys, Ltd.; suitable for general showing. *Miracles Take Longer.* 16 mm. Sound. Black-and-white. 22 min. 1960. Made by Vauxhall Motors, Ltd., in conjunction with the Luton and Dunstable Hospital; suitable for showing to undergraduate and postgraduate audiences and those interested in rehabilitation. *Edinburgh, 1959.* 16 mm. Sound. Colour. 20 min. 1959. Made by Film Surveys, Ltd.; suitable for general showing.

Copies of the following films have been purchased by the film library:

Thrombose et Haemostase Spontanée. 16 mm. Silent. Black-and-white. 18 min. 1958. Made by Dr. J. HUGHES, University of Liége; suitable for showing to undergraduate, postgraduate, specialist, and consultant audiences. *Open Heart Surgery (for Congenital and Acquired Heart Disease).* 16 mm. Sound. Colour. 21 min. 1959. Made by Professor J. C. CALLAGHAN, University of Alberta; suitable for showing to postgraduate, specialist, and consultant audiences.

B.M.S.A.'s 1960 Education Programme

The questionary to be sent this year by the British Medical Students' Association to all medical schools in the United Kingdom will deal with the teaching of pharmacology, therapeutics, and pharmacy. It will be in line with those completed last year on social medicine and on psychiatry.

Conference on Poliomyelitis

The National Foundation and the Danish Infantile Paralysis Association are sponsoring the fifth international poliomyelitis conference in Copenhagen on July 26, 27, and 28.

The opening session will deal with virology, the second will be a discussion of the present status of the killed or inactivated virus vaccines, and the third will cover all aspects of the live attenuated virus vaccine. Detailed information about the conference may be had from the Secretariat, Fifth International Poliomyelitis Conference, 5, Tuborqvei, Hellerup, Denmark.

Royal Edinburgh Hospital for Sick Children Centenary

The Royal Edinburgh Hospital for Sick Children has just celebrated its foundation 100 years ago with a service of thanksgiving and with a reception at the Royal College of Surgeons, Edinburgh.

Child health and the work of a children's hospital in those days must be viewed, as Professor R. W. B. ELLIS says in an article in *The Scotsman* (February 20), against the contemporary background of social evil and misery: in 1860 the Water of Leith was an open sewer, two cholera epidemics had recently occurred, and a third was to follow. Louse-borne typhus and typhoid were common, and in 1862 there was an outbreak of smallpox. In the

[*Royal College of Surgeons of Edinburgh*

Tron area the population density was 646 per acre compared with to-day's Edinburgh average of 13.9. Of every 1,000 infants born in Edinburgh a century ago 146 died before their first birthday—the corresponding figure to-day being 25. Pauper relief was fixed at a level which, as the town's first medical officer, Dr. H. LITTLEJOHN, put it, was only intended to allow of life being maintained at "a legal flicker." Against such a background the faith and vision involved in founding a children's hospital were considerable. The hospital's first surgeon was JOSEPH BELL, whose deductive powers and aquiline features have been immortalized by his student, A. CONAN DOYLE, in the character of Sherlock Holmes. In an early photograph, shown here, Bell is seen treating a child at the hospital.

Visiting Professors at Postgraduate Medical School

The Postgraduate Medical School of London welcomes three professors from overseas to take part temporarily in the work of the department of surgery.

Dr. S. R. FRIESEN (professor of surgery, University of Kansas, U.S.A.) is spending a year in the department, as also is Mr. B. S. RAO (professor of operative surgery, Andhra Medical College, Visakhapatam, India). Dr. M. K. CHACHAVA (professor of surgery, University of Tiflis, Georgia, U.S.S.R.) is here for three months.

COMING EVENTS

Christian Medical Fellowship.—Mr. A. S. ALDIS, "Keeping Faith with the Patient," March 16, 8.15 p.m., at the Royal Commonwealth Society, Northumberland Avenue, London, W.C.2 (Craven Street entrance).

Association of Industrial Medical Officers.—89th meeting, London, March 25 and 26. Details from the Honorary Secretary, 47, Lincoln's Inn Fields, London, W.C.2.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.*1.

Medical and Biological Illustration.—Issued quarterly (£3 annually). The new issue (Vol. 9, No. 4) includes:

Oddities of Medical Photography. F. Ronchese.
A Colourful Prospect. P. Hansell.
Modern Processes of Colour Photography. R. J. Finn and J. H. Coote.
Lighting in Orthopaedic Medicine. R. Whitley.
Improved Photography of the Larynx. H. Wieland.
A Viewing-Box for Paper-Mounted Sections. N. H. Pierce and A. D. Morgan.
Reconstruction-modelling in Blotting-paper. B. Towers.

Archives of Disease in Childhood.—Issued bi-monthly (£4 4s. annually). The new issue (Vol. 34, No. 178) includes:

The Maintenance of Stability in the Newly Born. Part 2. Thermal Balance. R. A. McCance.
Foetomaternal Transfusion as a Cause of Neonatal Anaemia. William Krivit, Robert Goodlin, Newell Ziegler, and Roger Lienke.
Mediastinal Duplication of the Gut. J. Stanley Elwood.
Intestinal Obstruction in a Case of Duplication of the Terminal Ileum. J. A. Williams.
The Incidence of Inguinal Hernia in Newcastle Children. George Knox.
A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children. Part V. Patterns of Maternal Care (A Study of Child Rearing in Scotland). Cecil Mary Drillien.
Masculinization of a Female Foetus with Oestrogenic Effect. G. H. Valentine.
Addison's Disease with Hypofunction of the Parathyroid Glands. H. Szczepańska and J. Sapiecha.
The Effect of Calomel on Plasma Epinephrine in the Rat and the Relationship to Mechanisms in Pink Disease. Donald B. Check and Fannie Wu.
A Case of Arthrogryposis Multiplex Congenita with Lesions in the Nervous System. Malcolm Fowler.
The Effect of a Bronchodilator Aerosol on Ventilatory Capacity in Fibrocystic Disease of the Pancreas. Bryan Gandevia and Charlotte Anderson.
Congenital Bowing of the Long Bones: Report of a Case. A. D. Bain and Helen S. Barrett.
Biochemical Studies in Idiopathic Hypercalcaemia of Infancy. John O. Forfar, S. L. Tompsett, and W. Forshall.
Narcolepsy in a Child Under 7 Years Old. D. J. Salfield.
Book Reviews.
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SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, March 7

DENTAL AND MEDICAL SOCIETY FOR THE STUDY OF HYPNOSIS.—At Royal Society of Medicine, 8 p.m., Dr. B. D. Wyke: Some Recent Experiments in Hypnosis.

GUY'S HOSPITAL: PHYSIOLOGY THEATRE.—5.30 p.m., endocrine demonstration by Dr. A. T. Cowie: Gynaecomastia and Disorders of the Breast.

MANCHESTER MEDICAL SOCIETY.—At Manchester University Medical School (Physiology Theatre), 4.30 p.m., meeting of Fellows. Professor D. E. Denny-Brown (Harvard): The Nature and Treatment of Recurrent Transient Cerebrovascular Episodes.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. C. White: Abnormal Haemoglobins.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. Antoinette Pirie: Biochemistry of the Eye.

Tuesday, March 8

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—At 36, Harborne Road, Edgbaston, 8 p.m., Dr. G. M. Carstairs: Recent Research on the Rehabilitation of Schizophrenic Patients.

FOUNTAIN HOSPITAL.—5.30 p.m., subject: Piaget's Approach to Intellectual Development. Professor E. A. Peel: Growth of Thinking in Children; Dr. Mary Woodward: Applications to Mental Subnormality.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. Hodgson: Skin Hazards of Petroleum Engineering Oils.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. Denis Williams: Syndromes of Basilar Insufficiency.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.15 p.m., special university lecture in biochemistry by Dr. F. Sanger, F.R.S.: Amino Acid Sequences in Proteins.

MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Manchester University Medical School (Clinical Sciences Building), 8 p.m., Mr. D. K. Lennox: Some Observations on the Obstructed Colon.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Oliver-Sharpey Lecture by Dr. J. D. N. Nabarro: Pituitary and Adrenal Cortex in General Medicine.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Lecture Theatre, 5 p.m., Mr. Aleck Bourne: Troubles of Puberty.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. G. C. Knight: Cervical Spondylosis.

Wednesday, March 9

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Antibiotics and Fungous Infections.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. J. Prime: Asphyxia and Chronic Bronchitis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. D. M. Wallace: Cancer of the Bladder.

●LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRAMURAL STUDIES.—At Medical School, 8 p.m., Dr. W. H. Taylor: Biochemical Factors in Blood Diseases.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital Medical School, 8.30 p.m., annual general meeting.

MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Manchester University Medical School (Large Anatomy Theatre), 5 p.m., Dr. G. Discombe: Some Observations on Iron Deficiency.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4 p.m., Moynihan Lecture by Professor F. Orban: New Trends in the Treatment of Thrombo-angiosis (Buerger's Disease).

Thursday, March 10

ALFRED ADLER MEDICAL SOCIETY.—At Royal Society of Medicine, 8 p.m., Dr. A. Spencer Paterson: Conditioned Reflex in Psychiatric Treatment. A discussion will follow.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. D. Samman: Tuberculosis of the Skin.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL.—4.30 p.m., First Wiltshire Memorial Lecture by Dr. Terence East: Forty Years of Cardiology.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., pathological meeting.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Dr. A. G. Signy: Modern Views on the Anaemias.

NORTH-WESTERN THORACIC SOCIETY.—At Clinical Sciences Buildings, York Place, Manchester, 5 p.m., Dr. George Simon: Radiological Changes in Heart Disease.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Oliver-Sharpey Lecture by Dr. J. D. N. Nabarro: Pituitary and Adrenal Cortex in General Medicine.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor S. O. Aylett: Diffuse Ulcerative Colitis and its Treatment by Ileorectal Anastomosis.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. H. Paterson: postgraduate demonstration in neurology.

Friday, March 11

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. D. Samman: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. K. E. Jefferson: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. N. Asherson: Common Maladies of Childhood.

KEIGHLEY AND DISTRICT MEDICAL SOCIETY.—At Victoria Hospital, Keighley, 8.30 p.m., Presidential Address.

LEEDS UNIVERSITY MEDICAL SOCIETY.—At Littlewood Hall, General Infirmary at Leeds, 4.15 p.m., B.M.A. Lecture by Dr. Donald Hunter: Importance of Historical Perspective in Medicine.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.15 p.m., special university lecture in biochemistry by Dr. F. Sanger, F.R.S.: Amino Acid Sequences in Proteins.

LONDON UNIVERSITY.—At London Hospital Medical College, 5.30 p.m., special university lecture in medicine by Professor D. E. Denny-Brown (Harvard): Nature of Polymyositis and Related Muscular Diseases.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. J. B. Pennybacker: Intervertebral Disk Lesions. (2) 4 p.m., Dr. J. A. Fraser Roberts: Medical Genetics (V).

Saturday, March 12

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Addenbrooke's Hospital, Cambridge, postgraduate course for general practitioners. Symposium on Cardiovascular Disease. At Lecture Room B. *Morning:* 10.30 a.m., Dr. H. A. Fleming: Physiological Basis of Cardiac Signs; 11.30 a.m., Dr. Duncan Gregg: Thoracic Aortography in Cardiovascular Disease; 12.15 p.m., Dr. D. G. Chalmers: Anticoagulants and the Cardiac Patient; *Afternoon:* 2.15 p.m., Mr. B. B. Milstein: Demonstration of clinical cases (in Anteroom of Lecture Room B); 3.15 p.m., Dr. H. A. Fleming: Atrial Septal Defect, the Commonest form of Congenital Heart Disease; 4 p.m., Dr. Leslie B. Cole: Subacute Bacterial Endocarditis; 4.45 p.m., "Any Questions?"

Sunday, March 13

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m., clinical discussion for general practitioners. Seminar by Mr. S. E. Birdsall: Problems in Otolaryngology.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Hughes.—On February 19, 1960, at St. David's Wing, Royal Northern Hospital, London, to Dorothie and David Hughes, of Chelston, Triggs Lane, Woking, Surrey, a son—John.

Kennedy.—On February 19, 1960, to Ismene (formerly More), wife of Dr. C. Cotton Kennedy, Dunavon, Craigavad, Co. Down, a daughter.

MARRIAGES

Galloway—Bell.—On February 20, 1960, at the Methodist Church, Aberdeen, Dr. W. H. Galloway, of 312, Queen's Road, Aberdeen, to Elaine Elizabeth Bell, of "Friendville," Mannofield, Aberdeen.

Mukerji—Banerji.—On January 29, 1960, at Calcutta, India, Dilip Mukerji, M.B., B.S., D.A., to Miss Dipali Banerji, B.A.

DEATHS

Allison.—On January 31, 1960, at The Hawthorns, Hindley, Lancs, Stuart Frew Allison, M.B., Ch.B., D.P.H.

Barnes.—On February 18, 1960, Frank Barnes, M.S., F.R.C.S., of The Briars, Monyhull Hall Road, King's Norton, Birmingham, Warwicks, aged 90.

Dryland.—On February 2, 1960, Gilbert Winter Dryland, M.B., B.Ch., of Pholeea, Kington, Herefordshire.

Farmer.—On February 8, 1960, at his home, Rozelle, Littleton, Winchester, Hants, John Lumsden Farmer, M.B., Ch.B., D.P.H.

Feltham.—On January 31, 1960, at 122, Kolmer Road, Papatoetoe, New Zealand, Wilfrid John Feltham, M.D.Ed., D.P.H., aged 76.

Hanan.—On February 1, 1960, at Meadowcliff, Mevagissey, Cornwall, Hugh Grant Hanan, M.B., Ch.B.Ed.

Hynd.—On January 31, 1960, in hospital, Robert Spence Hynd, M.B., Ch.B., of 50, Wilton Road, Salford, Lancs.

Lucas.—On February 6, 1960, at 6, Hillburn Road, Wisbech, Cambs, George Humphrey Lucas, M.R.C.S., L.R.C.P., aged 85.

Russell.—On February 7, 1960, in Dublin, Edmund Neptune Russell, M.D., formerly of Alexandria, Egypt.

Todd.—On February 5, 1960, Kenneth Waller Todd, M.R.C.S., L.R.C.P., D.T.M., of 1, Netherford Road, London, S.W.14, late of Ghana and Papua, aged 59.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Vitamin C for Colds

Q.—*Is there any evidence to support the widespread belief that a common cold may be aborted by taking strong doses of vitamin C on the first day of the attack?*

A.—The belief that vitamin C has a beneficial effect on the common cold dies hard. There have been a number of good clinical trials in this country,[1] in the U.S.A.,[2 3] and in Scandinavia[4] in which the value of ascorbic acid both as a prophylactic and as a therapeutic drug has been tested. These trials have been carried out on inmates of institutions, on university students, and on conscripted soldiers. None of them has produced any convincing evidence that, in subjects whose normal diet contains adequate amounts of vitamin C, ascorbic acid, either when taken daily during the winter months or when taken in large doses at the onset of the clinical features of a cold, has a significant effect when compared with a placebo. The trial which is most germane to the present question is that carried out by some American workers.[3] They asked volunteer students to report as early as possible after the onset of symptoms of a cold. 298 cases were observed; the treated group (179) were given 1 g. of ascorbic acid immediately and the 119 controls the same amount of citric acid. Similar instructions on the general management of the cold were given to both groups. They were seen again the following day and the dose of ascorbic acid or citric acid was repeated. The results were assessed at 48 hours. The assessment was based on whether the cold developed in the normal way or appeared to be aborted. In patients in whom the initial symptoms were entirely pharyngeal there was no difference between the treated and the control groups. In those in whom the initial features were both nasal and pharyngeal a rather greater number of the colds in the group who had received ascorbic acid failed to develop but the difference between the two groups was not statistically significant.

REFERENCES

1 Glazebrook, A. J., and Thomson, S., *J. Hyg.*, 1942, **42**, 1.
2 Cowan, D. W., Diehl, H. S., and Baker, A. B., *J. Amer. med. Ass.*, 1942, **120**, 1268.
3 Brown, W. B., Mahoney, F., Niedringhaus, A., and Locke, A., *J. Immunol.*, 1945, **50**, 161.
4 Dahlberg, G., Engel, A., and Rydin, H., *Acta med. scand.*, 1944, **119**, 540.

Genetic Risks of Radium-workers

Q.—*A patient who has worked for 20 years in close contact with radium is contemplating marriage. There are apparently no ill-effects from his work. Is there any danger of malformation to potential children?*

A.—Malformations in the newborn stem from two causes. There are developmental defects which may be due to a lesion induced in the developing embryo by physical (including *x*-ray examinations of the pregnant mother), chemical, or biological (e.g., maternal rubella) agents or to intrauterine factors. The causes of this group of defects occur after conception. Secondly, there are genetically determined defects due to dominant, sex-linked, or autosomal recessive genes. The responsible genes are determined before conception; they may be inherited, or be the results of spontaneous or induced (e.g., by radiation) mutation. Perhaps some 4% of live-born children have some major or minor genetically determined "defect,"[1] the vast majority of these being due to inheritance. Provided a person occupationally exposed to radiation does not accumulate more than 50 r to the gonads by the age of 30, or exceed the permissible annual average dose of 5 r thereafter, he need feel no "undue concern for himself or his offspring"[2]—that is, his likelihood of siring a child with developmental defect is not greater with the present methods of detection than for the normal person.

REFERENCES

1 *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*, 1958. New York.
2 *The Hazards to Man of Nuclear and Allied Radiations*, 1958. H.M.S.O., London.

Squint and Mental Development

Q.—*Is a pronounced convergent squint in a small baby likely to retard its mental development? If the cause of the squint is remediable surgically, how soon is it advisable to operate?*

A.—There is no scientific proof that a pronounced convergent squint in a small baby is likely to retard its mental development, provided that one or other eye is not so convergent as to prevent fixation in the primary position.

In answer to the second question, it is fair to say that in the majority of cases of squint a satisfactory cosmetic result can be obtained by surgical means, unless the squint is associated with some gross neurological or other disorder. With regard to the actual time of operation, opinions vary considerably, but there is much to be said for overcoming the physical deformity of the squint before the child becomes socially aware of his deformity and before serious education is begun. This remark, of course, applies only to those cases of squint which cannot be controlled by correction of the refractive error.

One should add that perhaps the most important thing in the treatment of squint is to ensure that the child grows up with two good seeing eyes, thus occlusion of the fixing eye in order to develop the squinting eye may be of paramount importance in the early stages.

NOTES AND COMMENTS

Chapped Hands.—Dr. J. CURLEY (Holywell, Flints) writes: I refer to "Any Questions?" of January 30 (p. 363). A simple and effective remedy is to apply liberally a hand cream on retiring and wear cotton gloves while sleeping.

Blepharitis.—Mr. M. J. GILKES (Brighton) writes: With reference to the reply given by your expert to a question on the treatment of blepharitis ("Any Questions?" January 30, p. 363), there is considerable evidence that the reduction of scalp dandruff by the use of selenium shampoos is often of great value, and a selenium-containing oculentum is well worth a trial in refractory cases. In some of these there is evidence that the *Pityrosporum ovale* is a contributory cause, and certainly its organisms can often be found if looked for.

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